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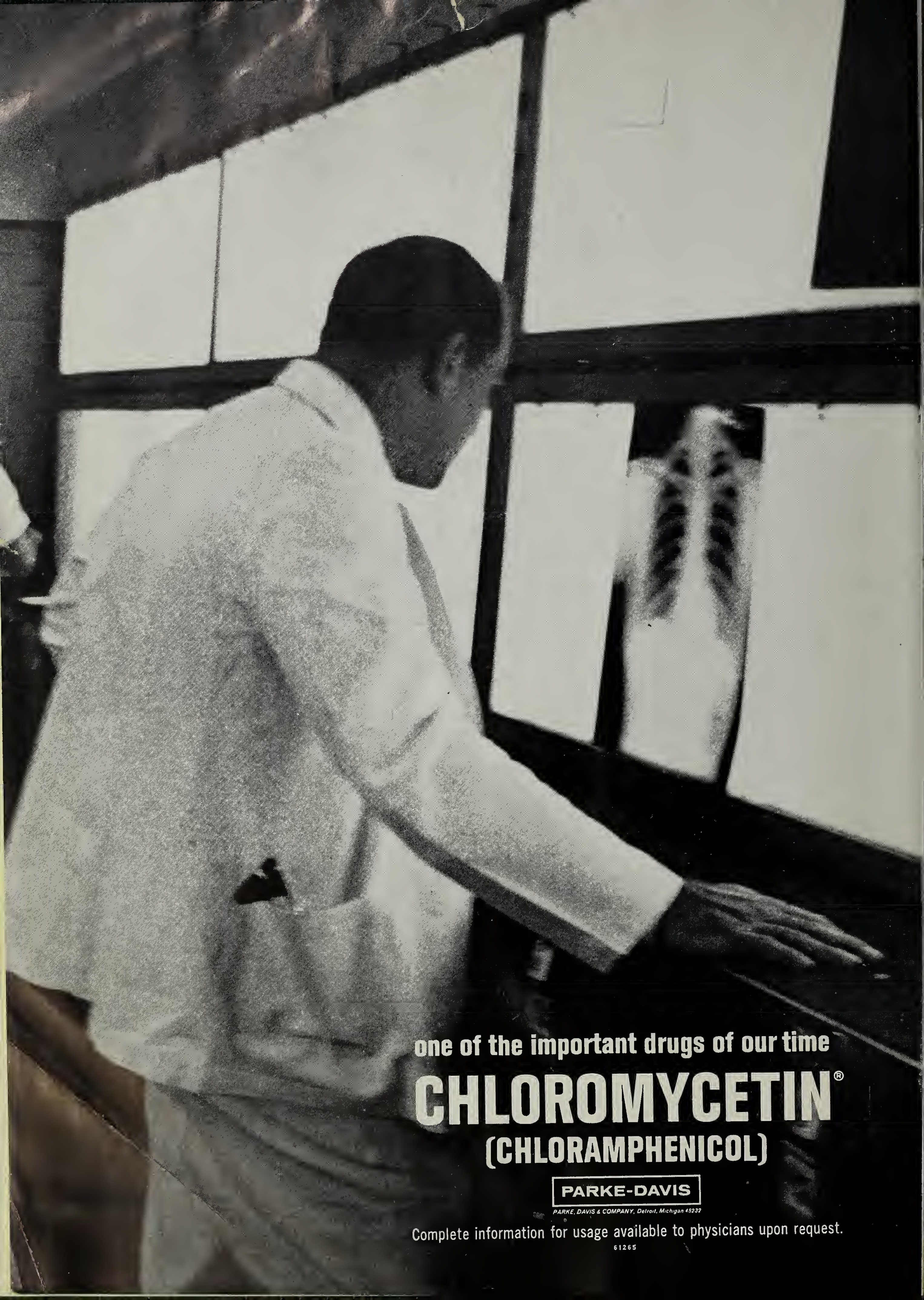

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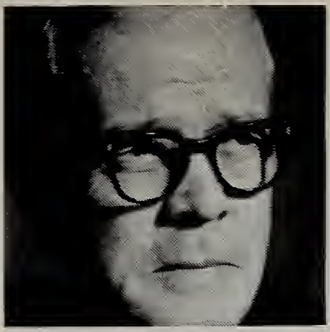

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Edmund L. Keeney, La Jolla	1968
Stuart C. Knox, Hollywood	1968

Committee on Maternal and Child Care

Leland B. Blanchard, San Jose	1966
James W. Ravenscroft, San Diego	1966
Russell W. Mapes, Beverly Hills	1967
Keith P. Russell, Los Angeles (Chmn.)	1967
Forrest H. Howard, Garden Grove	1967
Charles M. Blumenfeld, Sacramento	1968
Herbert A. Holden, San Leandro	1968

Committee on Cancer

Burt L. Davis, Palo Alto	1966
Paul C. Samson, Oakland	1966
John W. Cline, San Francisco	1967
Robert W. Jamplis, Palo Alto	1967
David A. Wood, San Francisco (Chmn.)	1967
John G. Walsh, Sacramento	1968
John G. Moore, Los Angeles	1968

SUBCOMMITTEE ON CANCER EDUCATION: Sol R. Baker, Beverly Hills; Robert W. Jamplis, Palo Alto (Chmn.); Maurice Galante, San Francisco; Justin J. Stein, Los Angeles.

SUBCOMMITTEE ON TUMOR TISSUE REGISTRY: John W. Cline, San Francisco (Chmn.); Lewis W. Guiss, Los Angeles; James E. Kahler, Los Angeles; Carl M. McCandless, San Francisco; Weldon K. Bullock, Los Angeles.

SUBCOMMITTEE ON CONSULTATIVE TUMOR BOARDS: Bert L. Halter, San Francisco; Carl L. Moore, Bakersfield; Victor Richards, San Francisco; John G. Walsh, Sacramento (Chmn.).

Committee on Dangerous Drugs and Adverse Drug Reactions

Charles H. Cutler, Sacramento	1966
Russell J. Tat, San Francisco	1966
Edward R. Bloomquist, Glendale	1967
Ralph O. Wallerstein, San Francisco	1967
John F. Murray, Fresno (Chmn.)	1968

SUBCOMMITTEE ON DANGEROUS DRUGS: Edward R. Bloomquist, Glendale; Norman A. Gale, San Diego; Edward T. Jewett, Santa Rosa; William F. Quinn, Los Angeles (Chmn.); Helen B. Weyrauch, San Francisco.

CONSULTANT: Ralph Weilerstein, Berkeley

* * *

BUREAU OF *Research and Planning*

Abe E. Berman, Sacramento
James C. Doyle, Beverly Hills
H. Russell Fisher, Glendale
Franklin F. Ham, Van Nuys
Paul I. Hoagland, Pasadena
James R. Powell, Stockton (Secty.)
John T. Saidy, San Mateo
John J. Sheehy, Riverside
Samuel R. Sherman, San Francisco (Chmn.)
Richard L. Taw, Los Angeles
EX-OFFICIO:
Ralph C. Teall, Sacramento
James C. MacLaggan, San Diego
Carl E. Anderson, Santa Rosa
CONSULTANT: Gerald W. Shaw, Santa Monica

* * *

COMMISSION ON *Professional Welfare*

Bert L. Halter, San Francisco
George K. Herzog, Jr., San Francisco (Chmn.)
Edward Liston, Palo Alto
J. Norman O'Neill, Los Angeles
Dan Tucker, Oakland
Francis E. West, San Diego
James H. Yant, Sacramento (Secty.)

Committee on Physicians Group Insurance

Homer C. Pheasant, Los Angeles	1966
Robert J. Westcott, El Centro	1967
Robert X. DeMangus, Glendale	1967
John B. Long, Sacramento	1967
George K. Herzog, Jr., San Francisco (Chmn.)	1968
Arthur Kirchner, Los Angeles	1968

Liaison Committee to Medical Schools

Bert L. Halter, San Francisco (Chmn.)	1966
Alonzo Neufeld, Los Angeles	1966
Samuel R. Irvine, Beverly Hills	1967
Francis E. West, San Diego	1967
Frank J. Novak, Menlo Park	1968
Stanley Cowell, Los Angeles	1968

EX-OFFICIO:
Ralph C. Teall, Sacramento
James C. MacLaggan, San Diego
Carl E. Anderson, Santa Rosa

Medical Review and Advisory Committee

Donald Donisthorpe, Los Angeles	1966
Eugene M. Webb, San Francisco	1967
James H. Yant, Sacramento (Chmn.)	1967
John Dillon, Los Angeles	1968

Liaison Committee to State Bar of California

Harold E. Wilkins, Downey	1966
Henry A. Brown, San Mateo	1966
David Rubsamen, Berkeley	1967
John V. Fiore, Westchester	1967
Francis E. West, San Diego (Chmn.)	1968
Carl Goetsch, Berkeley	1968

* * *

COMMISSION ON *Allied Health Professions and Services*

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Forest J. Grunigen, Los Angeles (Chmn.)
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Thomas W. Ledwich, Napa
Wayne E. Pollock, Sacramento (Secty.)

Committee on Paramedical Personnel

Gerson R. Biskind, San Francisco	1966
Carroll B. Andrews, Sonoma	1966
Arthur A. Kirchner, Los Angeles (Chmn.)	1967
Frank C. Melone, Ontario	1967
Gregory Bard, San Francisco	1968
Elmer R. Jennings, Long Beach	1968

Committee on Other Professions

Wayne E. Pollock, Sacramento (Chmn.)	1966
John F. Murray, Fresno	1966
David Eder, Pasadena	1967
Burt L. Davis, Palo Alto	1967
C. Gerald Scarborough, San Jose	1968
William D. Evans, Los Angeles	1968

Liaison Committee to California Medical Assistants Association

Sanford E. Feldman, San Francisco	1966
Leon O. Burke, Sacramento	1967
John C. Brennan, Pico Rivera	1967
H. Russell Irwin, San Diego	1967
Peary Benn Berger, Inglewood	1968
Charlotte C. Baer, San Francisco (Chmn.)	1968

Committee on Medicine and Religion

Ronald D. Smith, Fresno	1966
Frank J. Glassy, Sacramento	1966
Albert E. Long, San Francisco	1967
Roger W. Barnes, Los Angeles (Chmn.)	1967
Max Nelson, National City	1968

Committee on Voluntary Health Agencies

Harold E. Wilkins, Downey	1966
J. Brandon Bassett, Oakland	1966
H. Mason Hohl, Beverly Hills	1967
Thomas W. Ledwich, Napa (Chmn.)	1968

* * *

Judicial COMMISSION

Douglas G. Campbell, San Francisco	1966
W. Philip Corr, Riverside (Secty.)	1966
L. E. Wilson, Anaheim	1966
Donald A. Charnock, Los Angeles (Chmn.)	1967
Albert E. Long, San Francisco	1967
Donald Cass, Hollywood	1967
Floyd O. Due, Oakland	1968
Sidney J. Shipman, San Francisco	1968
Francis E. West, San Diego	1968

* * *

COMMISSION ON *Hospital Affairs*

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Lucius L. Button, Santa Rosa
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Daniel W. Black, Castro Valley
Rush M. Blodget, Jr., Redding
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Lucius L. Button, Santa Rosa
Bert L. Halter, San Francisco (Chmn.)
J. Ralph Hughes, San Diego
Wm. Kenneth Jennings, Santa Barbara
David B. Kuris, Los Angeles
John C. Lungren, Long Beach
James W. Martin, Sacramento
William A. Newson, San Francisco
John T. Saidy, San Mateo
Wilfred J. Snodgrass, Santa Monica
Joseph W. Telford, San Diego

Committee on Health Facilities Planning

James W. Dalton, Santa Barbara	1966
Paul C. Doehring, Glendale	1966
Pierre Salmon, San Mateo	1966
Laurence A. Mosier, Garden Grove	1967
John W. Gates, Visalia	1967
Joseph W. Telford, San Diego	1967
Jean F. Crum, Downey	1968
Glenn A. Pope, Sacramento (Chmn.)	1968
Richard L. Taw, Los Angeles	1968

CONSULTANTS: John F. Murray, Fresno; Robert F. Schell, San Rafael.

* * *

Finance Committee

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Roger C. Isenhour, San Diego
Frank C. Melone, Ontario
Joseph W. Telford, San Diego
Malcolm C. Todd, Long Beach

Committee on Legislation

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Harold E. Wilkins, Downey
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Alexander Fraser, San Francisco
Elizabeth Mason Hohl, Los Angeles
Don C. Musser, San Francisco
George Wolf, Fresno
Dudley M. Cobb, Jr., Los Angeles

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Members who contemplate presentation of scientific papers should promptly address the secretary of the proper section at the address shown below.

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John S. O'Toole..........Chairman
3616 Main St., Riverside 92501
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2040 Forest Ave., San Jose 95128
Ernest J. Saslow..........Assistant Secretary
2011 - 18th St., Bakersfield 93301

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439 - 30th St., Oakland 94609
Thomas W. McIntosh..........Secretary
686 E. Union St., Pasadena 91101
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3585 - 4th Ave., San Diego 92103

Dermatology

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1120 Montgomery Dr., Santa Rosa 95405
Robert G. Walton..........Secretary
1700 McHenry Village Way, Modesto 95350
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405 N. Bedford Dr., Beverly Hills 90210

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J. Blair Pace..........Secretary
408 Cassidy St., Oceanside 92054
Alfred F. Kandlbinder..........Assistant Secretary
302 Via Paraiso St., Monterey 93940

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Albert G. Clark..........Secretary
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David B. Sheldon..........Assistant Secretary
1180 Fishe, Pacific Palisades 90272

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555 S. Flower St., Los Angeles 90017

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384 Post St., San Francisco 94108
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1216 Wilshire Blvd., Los Angeles 90017

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490 Post St., San Francisco 94102
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490 Post St., San Francisco 94102

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20103 Lake Chabot Rd., Castro Valley 94546
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679 S. Westlake Ave., Los Angeles 90057

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636 Harris St., Eureka 95501
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14619 Whittier Blvd., Whittier 90605

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Gregory Bard..........Chairman
UC Medical Center, San Francisco 94122
Rene Cailliet..........Secretary
4900 Sunset Blvd., Los Angeles 90027

Preventive Medicine

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Room 6007, 1350 Front St., San Diego 92101
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P.O. Box 871, Martinez 94554
Herbert H. Cowper..........Assistant Secretary
111 E. 1st St., Los Angeles 90012

Psychiatry and Neurology

George Y. Abe..........Chairman
Metropolitan State Hospital, Norwalk 90650
Werner M. Mendel..........Secretary
1934 Hospital Pl., Los Angeles 90033
Ames Fischer..........Assistant Secretary
401 Parnassus Ave., San Francisco 94122

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John C. Bennett..........Chairman
2200 Hayes St., San Francisco 94117
(St. Mary's Hospital)
Victor G. Mikity..........Secretary
1200 State St., Los Angeles 90033
Vernon R. Gee..........Assistant Secretary
2020 Court St., Redding 96001

Urology

Carl Burkland..........Chairman
5301 F St., Sacramento 95819
Carl K. Pearlman..........Secretary
1518 N. Sycamore, Santa Ana 92701
James L. Goebel..........Assistant Secretary
51 Loma Linda, Ross 94957

Delegates and Alternates

TO THE AMERICAN MEDICAL ASSOCIATION

DELEGATES		ALTERNATES
Samuel R. Sherman, San Francisco	(1964-1965)	Albert G. Miller, San Mateo
Henry Gibbons, III, San Francisco	(1964-1965)	A. B. Sirbu, San Francisco
John M. Rumsey, San Diego	(1964-1965)	Carl E. Anderson, Santa Rosa
Eugene F. Hoffman, Los Angeles	(1964-1965)	Edward H. Crane, Jr., Inglewood
Warren L. Bostick, Los Angeles	(1964-1965)	Walter H. Brignoli, St. Helena
J. B. Price, Santa Ana	(1964-1965)	Donald C. Dodds, Oakland
Ralph C. Teall, Sacramento	(1964-1965)	Robb Smith, Orange Cove
James C. Doyle, Beverly Hills	(1964-1965)	Homer C. Pheasant, Los Angeles
Wilbur G. Rogers, Glendale	(1964-1965)	Carl M. Hadley, San Bernardino
Charles B. Hudson, Oakland	(1964-1965)	Robert L. Watson, Jr., Los Angeles
John G. Morrison, San Leandro	(1965-1966)	Frederick Ackerman, Pleasant Hills
Arthur A. Kirchner, Los Angeles	(1965-1966)	Dudley M. Cobb, Los Angeles
Robert C. Combs, San Francisco	(1965-1966)	Emmett Rixford, San Francisco
J. Norman O'Neill, Los Angeles	(1965-1966)	William F. Quinn, Los Angeles
J. Lafe Ludwig, Los Angeles	(1965-1966)	Harold Kay, Oakland
Burt L. Davis, Palo Alto	(1965-1966)	Leon P. Fox, San Jose
Arlo A. Morrison, Ventura	(1965-1966)	Henry Brown, San Mateo
James E. Feldmayer, Exeter	(1965-1966)	Charles Grayson, Sacramento
O. W. Wheeler, Riverside	(1965-1966)	Wilbur Bailey, Los Angeles
Malcolm C. Todd, Long Beach	(1965-1966)	Alfred J. Murrieta, Jr., Los Angeles
J. E. Vaughan, Bakersfield	(1965-1966)	Joseph P. O'Connor, Pasadena
Francis E. West, San Diego	(1965)	Nicholas V. Oddo, Long Beach

(Delegates and Alternates to the AMA are elected for terms of two calendar years. Each office is scheduled for election at the Annual Session of the second year shown above.)

Other Organizations and Medical Schools

Board of Medical Examiners of the State of California

Secretary..........Raymond M. Wallerius, M.D.
1021 O Street, Room A547, Sacramento 95814
San Francisco..........455 Golden Gate Ave.
Room 4184 94102
Los Angeles..........107 South Broadway 90012
Sacramento..........1021 O Street, Room A547 95814

The Public Health League of California

Executive Secretary..........Ben H. Read
955 South Western Ave., Los Angeles 90006
Associate Executive Secretary..........E. E. Salisbury
693 Sutter Street, San Francisco 94102
San Francisco..........693 Sutter Street 94102
415 474-1061
Los Angeles..........955 South Western Ave. 90006
213 731-6397

Department of Public Health of the State of California

Director..........Malcolm H. Merrill, M.D.
2151 Berkeley Way, Berkeley 94704
Berkeley..........2151 Berkeley Way 94704
415 843-7900
Sacramento..........631 J Street 95814
916 442-4711
Los Angeles..........703 State Building 90012
213 620-2900

Medical Schools in California

University of California School of Medicine, Medical Center, San Francisco 94122. Dean: William O. Reinhardt, M.D.
Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto 94304. Dean: Robert J. Glaser, M.D.
University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. Dean: Roger O. Egeberg, M.D.
Loma Linda University School of Medicine, Loma Linda 92354. Dean: David Burdg Hinshaw, M.D.
University of California at Los Angeles, School of Medicine, Hilgard Avenue, Los Angeles 90024. Dean: Sherman M. Melinkoff, M.D.
California College of Medicine: 1721 Griffin Avenue, Los Angeles 90031. Dean: Warren L. Bostick, M.D.
University of California, San Diego, School of Medicine, La Jolla 92038. Dean: Joseph Stokes, III, M.D.

Roster — CALIFORNIA COMPONENT MEDICAL SOCIETIES

Society secretaries are requested to notify California Medicine promptly when changes are indicated in their roster information

ALAMEDA-CONTRA COSTA Medical Assn., 6230 Claremont Ave., Oakland 94618. Meets quarterly.
Carl Goetsch .... President
2915 Telegraph Ave., Berkeley 94705
Frederick W. Ackerman .... Secretary
6230 Claremont Ave., Oakland 94618

BUTTE-GLENN Medical Society, P. O. Box 1008, Chico 95927. Meets Fourth Thursday.
Arthur J. Rollins .... President
247 N. Villa St., Willows 95988
John Copeland .... Secretary
1345 Longfellow Ave., Chico 95926

FORTY FIRST Medical Society, 4775 Santa Monica Blvd., Los Angeles 90029.
Paul D. Yates .... President
844 Hermosa Ave., Hermosa Beach 90254
Jordan M. Phillips .... Secretary
11239 S. Lakewood Blvd., Downey 90241

FRESNO County Medical Society, 1118 Divisadero St., Fresno 93721. Meets Second Tuesday, 6:30 p.m., Sunnyside Country Club.
J. Cooper Collins .... President
3006 N. Fresno St., Fresno 93703
Jerome Radding .... Secretary
139 N. Thesta St., Fresno 93701

HUMBOLDT-DEL NORTE County Medical Society. Meets Second Thursday.
Stanwood S. Schmidt .... President
707 K St., Eureka 95501
Halvor J. Braafladt .... Secretary
311 G St., Eureka 95501

IMPERIAL County Medical Society. Meets Second Tuesday, 8 p.m., Pioneer Memorial Hospital, Brawley.
Robert H. Worthman .... President
239 S. 8th St., El Centro 92243
George Jaquith .... Secretary
116 N. Plaza St., Brawley 92227

INYO-MONO County Medical Society. Meets Fourth Tuesday except December, January, February.
D. L. Christenson .... President
380 N. Mt. Whitney Dr., Lone Pine 93545
W. Ray Hartwig .... Secretary
459 West Line, Bishop 03514

KERN County Medical Society, 2603 G Street, Bakersfield 93301. Meets Third Tuesday, 7:30 p.m., Society Office, 2603 G Street, except June, July, August.
Max H. Newman .... President
1420 Crestmont Dr., Bakersfield 93306
Theodore L. Bosonetto .... Secretary
2330 Truxton Ave., Bakersfield 93301

KINGS County Medical Society. Meets Second Thursday, 7:00 p.m. Place to be announced.
Dallas L. Paden .... President
1028 N. Douty St., Hanford 93230
Edwin E. Kerr .... Secretary
208 N. Douty St., Hanford 93230

LASSEN-PLUMAS-MODOC-SIERRA County Medical Society. Meets on call.
Robert C. Haggard .... President
P.O. Box 517, Loyalton 96118
Kenneth G. Korver .... Secretary
50 N. Roop St., Susanville 96130

LOS ANGELES County Medical Assn., 1925 Wilshire Blvd., Los Angeles 90057.
John A. Bullis .... President
1925 Wilshire Blvd., Los Angeles 90057
Harold E. Wilkins .... Secretary
1925 Wilshire Blvd., Los Angeles 90057

MARIN Medical Society, 1601 Second St., Suite 106, San Rafael 94901. Meets First Thursday, 7:00 p.m.
Ira H. Degenhardt .... President
707 C St., San Rafael 94901
Robert F. Schell .... Secretary
600 Mission Ave., San Rafael 94901

MENDOCINO-LAKE County Medical Society.
William W. Waring .... President
331 W. Perkins St., Ukiah 95482
Patrick R. Allanson .... Secretary
765 S. Dora St., Ukiah 95482

MERCED County Medical Society. Meets Fourth Thursday; meeting place changes.
John East .... President
652 W. 20th St., Merced 95340
Patrick J. Maloney .... Secretary
656 W. 20th St., Merced 95340

MONTEREY County Medical Society, P. O. Box 308, Salinas 93903. Meets First Thursday.
Robert P. Klinefelter .... President
505 E. Romie Lane, Salinas 93903
James W. Knight .... Secretary
601 E. Romie Lane, Salinas 93903

NAPA County Medical Society. Meets Second Wednesday, P. O. Box 658, Napa 94559
Donald E. Slaughter .... President
980 Trancas St., Napa 94558
Richard W. Neil .... Secretary
1375 Main St., St. Helena 94574

ORANGE County Medical Association, 300 S. Flower, Orange 92666. Meets First Tuesday, 7:00 p.m.
Henry V. Eastman .... President
661 W. 1st St., Tustin 92680
Wallace A. Gerrie .... Secretary
1901 Westcliff Dr., Newport Beach 92660

PLACER-NEVADA County Medical Society. Meets Second Wednesday.
H. William Shamhart .... President
1300 Douglas St., Roseville 95678
Arthur R. Weaver .... Secretary
701 High St., Auburn 95603

RIVERSIDE County Medical Association, 4175 Brockton Ave., Riverside 92501. Meets Second Monday, 7:30 p.m., Spanish Arts Gallery, Mission Inn.
John C Ivanoff .... President
4024 12th St., Riverside 92501
Richard W. Trotter .... Secretary
6876 Magnolia Ave., Riverside 92506

SACRAMENTO County Medical Society, 5380 Elvas Ave., Sacramento 95819. Meets Third Tuesday, 8:30 p.m. Location of meetings varies.
Donald P. Hause .... President
3965 J St., Sacramento 95819
James W. Martin .... Secretary
2811 L Street, Sacramento 95816

SAN BENITO County Medical Society. Meets once a month, except July and August. Time and place to be announced.
Kent S. Taylor .... President
1447 Grand Ave., Grover City 93433
Robert D. Quinn .... Secretary
535 Monterey St., Hollister 95023

SAN BERNARDINO County Medical Society, 1875 N. D St., San Bernardino 92405. Meets First Tuesday, 7:30 p.m., Harold's Club, Fontana.
Allen F. Sterling .... President
1277 D St., San Bernardino 92405
Nicholas P. Krikes .... Secretary
25060 Base Line, San Bernardino 92410

SAN DIEGO County Medical Society, 3427 - 4th Ave., San Diego 92103. Meets Second Tueseday. Location of meetings varies.
John W. Flaiz .... President
3427 4th Ave., San Diego 92103
W. C. Herrick .... Secretary
233 A St., San Diego 92101

SAN FRANCISCO Medical Society, 250 Masonic Ave., San Francisco 94118.
Edgar Wayburn .... President
490 Post St., San Francisco 94102
Nicholas D. Bonfilio .... Secretary
1548 Stockton St., San Francisco 94133

SAN JOAQUIN County Medical Society. Meets First Thursday, 8:15 p.m., 445 W. Acacia St., P. O. Box 230, Stockton 95201.
David Leon Green, Jr. .... President
2633 Pacific Ave., Stockton 95204
Dora A. Lee .... Secretary
2420 N. California St., Stockton 95204

SAN LUIS OBISPO County Medical Society. Meets Third Saturday, 7:00 p.m., Anderson Hotel, San Luis Obispo 93402.
Tibor Beresky .... President
100 Casa St., Suite B, San Luis Obispo 93401
Louis Zimmerman .... Secretary
1010 Murray Ave., San Luis Obispo 93401

SAN MATEO County Medical Society, 122 El Camino Real, San Mateo 94401. Meets Third Tuesday.
William G. Larsen .... President
104 St. Matthews Ave., San Mateo 94401
Stanford B. Rossiter .... Secretary
Sequoia Hospital, Redwood City 94062

SANTA BARBARA County Medical Society, 300 W. Pueblo St., Santa Barbara 93105. Meets Second Monday of the month, University Club, 1332 Santa Barbara St., Santa Barbara.
Nils Bolduan .... President
15 E. Arrellaga St., Santa Barbara 93105
Casimir Domz .... Secretary
317 W. Pueblo St., Santa Barbara 93105

SANTA CLARA County Medical Society, 700 Empey Way, San Jose 95128. Meets First Monday.
Richard S. Wilbur .... President
700 Empey Way, San Jose 95128
Gerald Besson .... Secretary
700 Empey Way, San Jose 95128

SANTA CRUZ County Medical Society, Meets every Second Month, Second Tuesday. Time, place to be announced.
Paul Roach .... President
1700 Mission St., Santa Cruz 95060
William Blade .... Secretary
1510 Seabright Ave., Santa Cruz 95062

SHASTA-TRINITY County Medical Society. Meets Second Monday of the month. Place to be announced.
Melvin L. Gumm .... President
1760 Gold St., Redding 96601
Faylon M. Brunemeier .... Secretary
2020 Court St., Redding 96001

SISKIYOU County Medical Society. Meets Sunday on call.
Rand Apgood .... President
746 S. Main St., Yreka 96097
Harry Chappell .... Secretary
Dunsmuir 96025

SOLANO County Medical Society. Meets Second Tuesday, 8:00 p.m., at different meeting places.
Harle B. Grover .... President
839 Louisiana St., Vallejo 94590
Richard D. Frank .... Secretary
1200 Marin St., Vallejo 94590

SONOMA County Medical Society, 576 B Street, Santa Rosa 95401. Meets Second Thursday.
Richard C. Barnett .... President
450 Pitt St., Sebastopol 95472
Tetsuro Fujii .... Secretary
1667 Bloomfield Rd., Sebastopol 95472

STANISLAUS County Medical Society, 303 Downey Ave., Modesto. Meets Third Tuesday of the month, 7 p.m., Hotel Covell, Modesto 95354.
Everett H. Johnson .... President
190 N. Thor St., Turlock 95380
Jeanne I. Miller .... Secretary
709 18th St., Modesto 95354

TEHAMA County Medical Society. Meets at call of President.
Lynn E. Wolfe .... President
75 Belle Mill Road, Red Bluff 96080
William L. Weirich .... Secretary
210 S. Main St., Red Bluff 96080

TULARE County Medical Society, 1640 West Mineral King, P. O. Box 16, Visalia 93278.
John A. Adamson .... President
403 N. L St., Dinuba 93618
John C. Williams .... Secretary
1640 West Mineral King, Suite 107, Visalia 93277

VENTURA County Medical Society. Meets Second Tuesday each month, 7:30 p.m., Los Posas Country Club, Camarillo.
Armando Pallais .... President
1532 Saviers Rd., Oxnard 93031
F. K. Helbling .... Secretary
3081 Loma Vista Rd., Ventura 93003

YOLO County Medical Society. Meets First Wednesday.
Samuel C. Houston .... President
3 Court St., Woodland 95695
William T. Robinson .... Secretary
650 3rd St., Woodland 95695

YUBA-SUTTER-COLUSA County Medical Society.
James D. Williams .... President
389 Del Norte Ave., Yuba City 95991
Norman K. Noordhoff .... Secretary
320 G St., Marysville 95901

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Vice-Chairman of the Board	Burt L. Davis
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Assistant Treasurer	Mr. John Cowee

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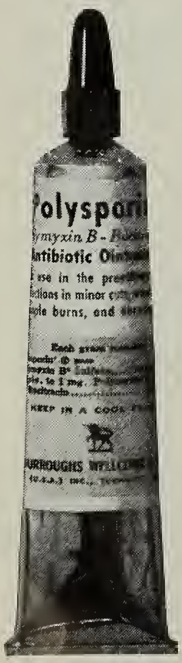

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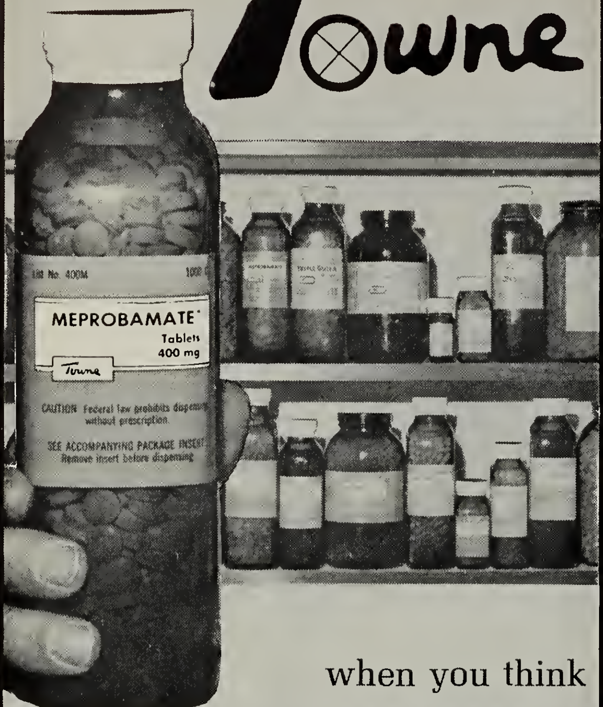
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Annual Report on Medical Licensure

The 63rd annual report on medical licensure statistics appears in the June 7 *Journal of the American Medical Association.*

A total of 7,911 physicians were newly added to the licensed medical profession in the U.S. in 1964, according to the report by the AMA Council on Medical Education.

There were 6,605 newly licensed U.S. and Canadian medical school graduates and 1,306 graduates of medical faculties in other countries. Newly licensed foreign medical graduates have gradually decreased each year since the high of 1,626 in 1959. In recent years, about one quarter of foreign-trained graduates issued first licenses have been U.S. citizens who attended medical schools outside the U.S. and Canada.

A total of 17,885 licenses to practice medicine and surgery were issued during 1964 by 55 authorized boards in the U.S. and its territories. This total included first licenses for new physicians, licenses for physicians moving to other states, and licenses for foreign-trained physicians.

Of all licenses issued during 1964, 7,166 were granted after successful written examination and 10,719 by reciprocity and endorsement of state licenses or the certificate of the National Board of Medical Examiners.

As of Dec. 31, 1964, there were 284,271 physicians in the U.S. (excluding 1,740 temporarily in other countries).

Licensing board examination failures in 1964 totaled 1,181. The percentage of failures in the written examinations of graduates of approved U.S. medical schools was 1.7; of graduates of approved Canadian medical schools, 7.8 per cent failed. Graduates of schools of osteopathy admitted to medical licensure examination in several states had 9.4 per cent failures, and 31.8 per cent of foreign-trained physicians examined for medical licensure failed. The total percentage of failures was 13.4 per cent, about the same as 1963.

A second section of the Council's report pertains to examination results and endorsement of credentials sponsored by 24 boards of examiners in the basic sciences in 23 states and the District of Columbia.

A third section deals with examinations given by the National Board of Medical Examiners. In 1964, the District of Columbia, Guam, Puerto Rico and 42 state boards issued 4,730 licenses to practice medicine on the basis of endorsement of the National Board certificate.

The fourth and concluding section of the report summarizes results of examinations given to for-

(Continued on Page 32)

How NALLINE® helps to keep the lid on drug addiction in California
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References: 1. Brown, T. T.: The Enigma of Drug Addiction, Springfield, Ill., Charles C Thomas, 1961, pp. 287-334. 2. Chesnick, R. D.: Med. Times **90**:247 (March) 1962. 3. Narcotic Addiction Symposium: New York Med. **18**:562 (Aug. 20) 1962.

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Annual Report on Medical Licensure

(Continued from Page 16)

eign-trained physicians by the Educational Council for Foreign Medical Graduates.

The report was compiled by the AMA staff under the supervision of Walter S. Wiggins, M.D., secretary of the Council; A. N. Taylor, Ph.D., associate secretary, and Henry R. Mason, M.P.H., assistant secretary.

W. Clarke Wescoe, M.D., chancellor of the University of Kansas, is chairman of the Council on Medical Education. Warde B. Allan, M.D., Baltimore, Md., is vice chairman.

Potassium May Cause Ulcerations

The small-bowel ulcerations suffered by a very small percentage of patients who have taken thiazide drugs may have been caused by the potassium supplement in the pills, suggests a report in the May 31 *Journal of the American Medical Association.*

There recently has been a "sudden and startling increase" in the incidence of these ulcerations, the report notes.

The article stresses, however, "there is no clinical or experimental evidence indicating the need for any limitation of the use of thiazide diuretics alone."

The thiazides, which are given to stimulate urine secretion, do not appear to play any part in the production of the ulcers, said the report by six physicians at the Jewish Hospital, Brooklyn, N.Y.

Instead, the fault may lie with the potassium chloride sometimes included in thiazide pills to help replace potassium lost in heavy urine flow.

This potassium chloride is released in the intestinal tract when a coating surrounding it dissolves. The ideal coating, the report noted, is one which maintains the tablet until it reaches the small intestine, and then permits rapid release of the drug.

"Ironically, the more nearly a particular coating approaches this goal, the more apt it is to result in ulceration," the report said.

The article reported research in which tablets of thiazide, potassium and tablet coatings were implanted in dogs' intestines.

Heavy concentrations of potassium in small areas of the dogs' intestines caused the most injury, the report said.

The amount of injury varied, but was roughly related to the quantity of potassium used. Neither thiazide nor the coating surrounding the pill were found to cause damage, the report said.

Authors of the article are Scott J. Boley, M.D., Leon Schultz, M.D., Harvey Krieger, M.D., Solomon Schwartz, M.D., Alberto Elguezabal, M.D., and Arthur C. Allen, M.D.

California
Medicine

Enterovirus Infections:

Etiologic, Epidemiologic and Clinical Aspects

DOROTHY M. HORSTMANN, M.D., *New Haven, Connecticut*

■ *The term* enteroviruses *was introduced in 1957 to bring together in one large family the polioviruses, Coxsackie A and B and echoviruses, all agents for which the human alimentary tract is the natural habitat. At present more than 60 distinct members are recognized: three polioviruses, 24 Coxsackie A, six Coxsackie B and 30 echoviruses. The list of new members, particularly in the* ECHO-*group, grows regularly. The viruses are frequently widely disseminated in the summer and fall of the year, circulating chiefly among young children, causing both apparent and inapparent infection. The enteroviruses are responsible for a wide spectrum of clinical manifestations, including non-specific febrile illness, sometimes with rash, aseptic meningitis, paralytic disease, respiratory infections, pericarditis and myocarditis. There is considerable overlap in biologic behavior, and the same syndrome can be induced by many different agents.*

In a few instances the clinical pattern is distinct enough to suggest the group of agents involved. Thus, herpangina is associated with the Coxsackie A viruses and epidemic myalgia (devil's grip) with the Coxsackie B group. Paralytic disease is caused primarily by the polioviruses, but recently it has been found that other members, particularly the Coxsackie B viruses and Coxsackie A7 can also cause "paralytic poliomyelitis."

The ultimate potential of enteroviruses in terms of central nervous system disease and other manifestations is unpredictable. Great variety in terms of clinical and epidemiologic behavior of known and "new" viruses has been the pattern in the past, and is likely to continue.

THE ENTEROVIRUSES are an extraordinarily versatile family of viruses. Although illnesses which they cause are more often of concern to pediatricians than to internists, the many discoveries over the past 15 years relating to this group of agents have general interest and application in virology and in clinical medicine. In the following discussion, I shall review briefly something about the enteroviruses themselves, the epidemiology of infections caused by them and some of the clinical problems which they present.

Etiology

The term *enteroviruses* was introduced in 1957 to bring together in one family the polioviruses, Coxsackie A and B, and echoviruses, all agents for which the alimentary tract is the natural habitat.[4] The characteristics which these agents have in common are summarized in Table 1. Unlike the

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From the Departments of Epidemiology and Public Health and Pediatrics, Yale University School of Medicine, New Haven.

Presented before the Section on Internal Medicine at the 94th Annual Session of the California Medical Association, San Francisco, March 28 to 31, 1965.

bacterial flora, they are transient inhabitants of the alimentary tract—that is, they cause acute infection, are excreted for a period of weeks, and disappear, leaving the host relatively immune to reinfection with the homologous virus type. All are small (15 to 30 mμ) ribonucleic acid (RNA) viruses which exist in multiple antigenic types. They lack essential lipids and are therefore resistant to ether and other organic solvents. On the basis of shared physical and biochemical properties, the enteroviruses, along with the rhinoviruses (the chief agents causing the common cold in adults) are now classified together as the *Picornaviruses* (Table 2) The *pico* in the name refers to their very small size, and the RNA indicates their nucleic acid type. In addition to picornaviruses of human origin, there are a number of similar agents which have been isolated from lower animals. These include the virus of hoof and mouth disease, Teschen disease of swine, Theilers virus, enteroviruses of monkeys, cattle and swine, as well as bovine and equine rhinoviruses.

The story of the enteroviruses is a good illustration of the crucial role of methodology in scientific research, for each burst of discovery in this field has depended upon the development of a new technique. It is astonishing to reflect that before 1948 when the monkey was the major test system used for isolation of viruses from patients with central nervous system (CNS) disease, polioviruses were the only known members of the enterovirus group. In 1948 the use of suckling mice for testing fecal specimens led Dalldorf and Sickles[5] to their discovery of the Coxsackie viruses, of which 24 group A and 6 group B are now known. Subsequently, the introduction of tissue culture methods resulted in the discovery of the continually growing family of echoviruses (the ECHO stands for enteric cytopathogenic human orphans) so named because in the beginning it was not known whether or not they were associated with human illness. Some 30 echovirus types are now recognized. By and large, they do not induce disease when inoculated into animals, and their *sine qua non* is cytopathogenicity for primate cells in tissue culture. The discovery of the echoviruses is a direct result of the introduction of practical tissue culture techniques in 1948 by Enders, Weller and Robbins.

The diagnosis of the specific etiologic agent of enterovirus infections can be accomplished only in the laboratory. Virus isolation is the most satisfactory means, and the agents are recovered readily from throat swabs and fecal specimens by inoculation into tissue cultures of primate cells, or in the case of most Coxsackie A viruses, by inoculation of suckling mice. Infections induce neutralizing and complement-fixing antibody responses, but because of the multiplicity of antigenic types, serologic diagnosis in the absence of virus isolation is rarely feasible.

TABLE 1.—*Characteristics of Enteroviruses (Poliovirus, Coxsackie,* ECHO

1. Transient inhabitants of the alimentary tract.
2. Multiple antigenic types.
3. Small particle size—15 to 30 mμ.
4. Ribonucleic acid (RNA) core.
5. Lack essential lipids and are therefore resistant to ether and other organic solvents.
6. Stabilized against thermal inactivation by divalent cations (Mg^{++}, Ca^{++}).

TABLE 2.—*Picornaviruses (Pico-RNA)*

	Serotypes
A. *Picornaviruses of human origin:*	
1. Enteroviruses	
(a) Polioviruses	3
(b) Coxsackie A	24
(c) Coxsackie B	6
(d) ECHO	32 (−2)*
2. Rhinoviruses	53 (+)
3. Unclassified	Many
B. *Picornaviruses of lower animals:*	
Foot and mouth disease virus	
Enteroviruses (of cattle, swine, monkeys, mice)	
Rhinoviruses (of cattle, horses, etc.)	

*Two echoviruses have been removed from the group and reclassified, ECHO-10 as reovirus type 1, and ECHO-28 as rhinovirus type 1.

Epidemiology

In addition to sharing the same physical and biochemical properties, the enteroviruses behave similarly epidemiologically (Table 3). In temperate zones they have a sharp seasonal incidence with a peak in the summer and fall. In the tropics and in semi-tropical areas, however, they are endemic the year round, often to an extraordinary degree. The seasonal incidence in temperate climates is similar to the pattern for other enteric infections, but the reasons for this behavior are poorly understood. The viruses are often widely disseminated in a community during a given period; frequently more than one agent is active at the same time, the types of illnesses induced being similar whatever the agent. In spite of wide prevalence, however, there may be relatively little clinical disease, for in general the majority of enterovirus infections are inapparent, and only occasionally do they induce clinical symptoms and

TABLE 3.—*Enterovirus Infections—Epidemiologic Features*

1. Seasonal incidence: summer-fall in temperate climates; prevalent the year round in tropical and subtropical areas.
2. Inapparent infections commoner than clinical disease.
3. Modes of virus dissemination: fecal-oral, and pharyngeal-oropharyngeal.
4. Virus dissemination influenced by sanitary environment.
5. Age incidence: primarily in young children; older children and adults often immune as a result of previous inapparent infection.

signs. Thus for poliovirus infections, the most thoroughly studied of the group, there is evidence that even during severe epidemics there are at least a hundred inapparent infections for every paralytic case. There is some variation depending upon the agent involved, but the clinically ill segment of the population usually represents only the visible part of the iceberg; beneath the surface is a far larger segment in which the viruses circulate silently, chiefly among young children.

Whether an individual experiences an apparent or an inapparent infection, however, he seems to be an equally good source of enterovirus spread. These infections are highly contagious, particularly in the family setting. The incubation period is short, and several days after exposure and as long as a week before onset of symptoms, virus is often present in the blood, throat and feces (Chart 1). Excretion from the throat continues for seven to ten days, and from the feces for several weeks or more. The period of greatest infectiousness appears to be around the time of onset, when virus is shed from the throat, and is excreted in the feces in maximum quantities. There is some question as to whether transmission is primarily from the pharynx of one person to the oropharynx of another, or whether the fecal-oral route is the main one. At present, based on evidence accumulated as a result of widespread use of inactivated Salk-type poliovirus vaccine, it appears that one or the other of these routes may dominate, depending upon certain environmental factors.[2] Thus in populations with high standards of hygiene and sanitation, pharyngeal-oropharyngeal transmission seems to be the more important, while in populations living in poor sanitary environments, major dissemination occurs by the fecal-oral route.

Socio-economic factors and environmental sanitation have a decided influence on the degree of dissemination as well as on the mode of spread of enteroviruses. Surveys of populations living under crowded conditions in poor sanitary environments indicate that as high as 60 per cent of normal children under 2 or 3 years of age are infected with and excreting one or more enteroviruses at any given time.[22] Excretion rates among children of the same age living in a more favorable environment are much lower, even during periods of epidemic prevalence.[7] Age has a pronounced effect on ability to spread enteroviruses: young children under 2 years are the most effective dis-

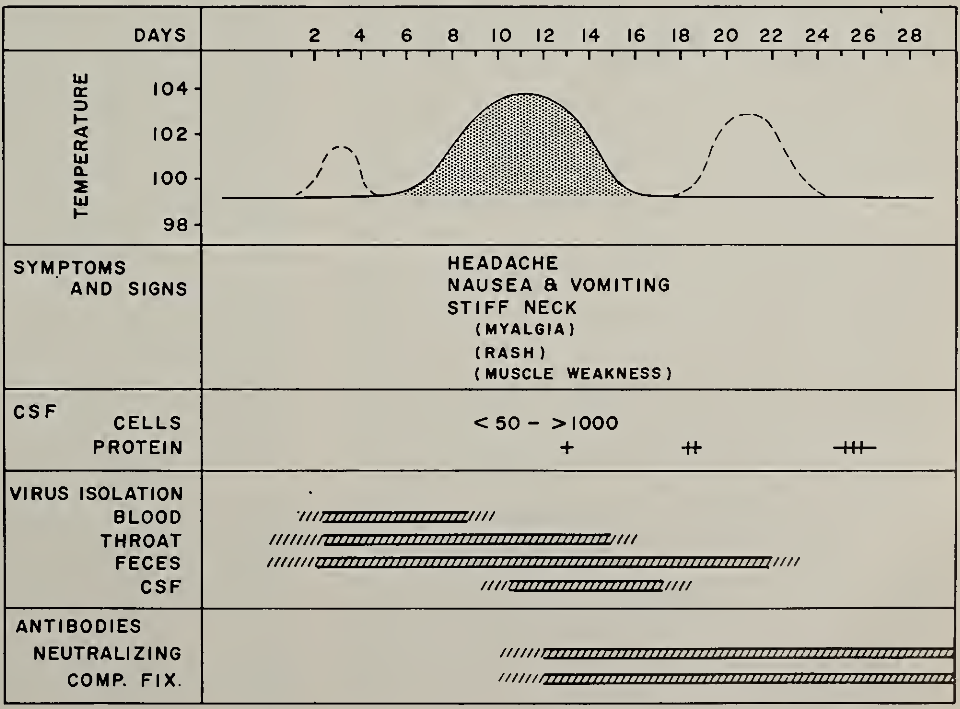

Chart 1.—Schematic diagram of the course of enterovirus infections of the central nervous system. Whether the clinical response is mild or severe, patterns of virus excretion and antibody rises are similar. Temperature curves with interrupted lines indicate that: (1) a "minor illness" followed by several days of well-being may precede the onset of CNS symptoms and signs; and (2) in certain epidemics (e.g. with ECHO 9 virus) recurrence of fever and meningeal signs may occasionally be observed after apparent recovery.

TABLE 4.—*Clinical Syndromes (Other Than Neurologic) Associated with Enterovirus Infections*

Syndrome	*Associated Agents*
Minor febrile illness (nonspecific)	Polioviruses Coxsackie A Coxsackie B Echoviruses
Herpangina	Coxsackie A1, 2-4, 6, 8, 19
Hand, foot, and mouth disease	Coxsackie A5, 16
Acute lymphonodular pharyngitis	Coxsackie A10
Neonatal myocarditis	Coxsackie B1-5
Myocarditis and pericarditis in children and adults	Coxsackie B1-5
Pleurodynia	Coxsackie B1-5 Echovirus 6, 8, 9
Acute respiratory tract infections URI (upper respiratory illness)	Coxsackie A21, 24 Coxsackie B1-5 Echovirus 11, 20
Bronchopneumonia	Coxsackie A9 Coxsackie B4, 5
Enteritis (diarrheal disease)	Echovirus 11, 14, 17, 18, and ? others; ? Coxsackie viruses

seminators, probably because of their unhygienic habits whatever the external sanitary environment. As with polioviruses, widespread infection early in life results in a solidly immune older population in which epidemics of clinical disease do not occur. In populations living under optimum conditions of sanitation and hygiene, however, young children are protected from immunizing infections in early life, and the resulting build-up of a susceptible older population provides fertile soil in which epidemics may start when virulent strains are introduced.

Age has a good deal to do with both susceptibility to infection and to the type and severity of clinical manifestations. As with so many viral infections, the young adult experiences a more severe disease than does the young child. With poliomyelitis, this became increasingly apparent in the United States between the years 1930 and 1955, during which there was a shift in the pattern of age distribution of paralytic cases toward an ever increasing incidence in older children and young adults. Whether this same shift will occur with other enterovirus infections is not known, but there are indications that it is not an unlikely possibility. Thus in the large epidemics of ECHO-9 virus infections which swept the United States in 1957-58, as high as 50 per cent of adults were susceptible and many became ill when exposed in the family setting.[26] In the 1960 epidemic of aseptic meningitis in Minnesota, associated with echovirus type 30, the highest attack rate was in the 20 to 24 age group, which suggests that this agent was new to the area, or at least had not been circulating for many years.[15]

Clinical Aspects

Turning to the clinical features of infections with enteroviruses, these are as complex, diverse and ever-changing as other aspects. Discovery of new techniques, "new" viruses and "new" clinical syndromes has been—and is likely to continue to be—the pattern. By and large there are few specific *diseases* associated with enteroviruses, but instead, a variety of *syndromes* (Table 4, 6). Any one syndrome can be caused by a number of different agents, and any one agent is capable of inducing a variety of clinical syndromes. The specific etiologic diagnosis of an illness can be made only in the laboratory, and here too there are difficulties, for recovery of an agent does not necessarily mean that the agent caused the patient's illness since inapparent infections with enteroviruses are so common. Controlled studies and the accumulated experience over the past 15 years, however, have established the role of these agents in causing certain syndromes. These will be reviewed briefly.

Nonspecific febrile illness; enterovirus exanthems

The commonest syndrome associated with enteroviruses is the non-specific febrile illness. Probably all 63 of the known enteroviruses can cause this. The "minor illness" or abortive form of poliovirus infection[23] is the classic example: a 24 to 48 hour illness with low grade fever, anorexia, sometimes sore throat and vomiting. The other agents commonly induce a similar clinical response. Many, or even most such infections are so mild that the physician is not called. But in recent years it has become apparent that enterovirus infections may be associated with skin eruptions,[1,19] and if the minor illness is accompanied by a rash, the patient is more likely to be seen by a physician. Table 5 indicates the enterovirus infections so far associated with rash, either commonly or occasionally. There are doubtless others, and as the list grows steadily it would seem likely that skin lesions can occur with most enterovirus infections under certain circumstances. The appearance of the rash is similar, no matter which agent is involved. The most common form is a maculopapular (rubelliform) eruption which is non-pruritic and does not desquamate. Sometimes petechial, vesicular, scarlatiniform or mixed forms appear. A given virus type may be associated with different eruptions even during the same epidemic, and there is also variation from epidemic to epidemic, as has been reported with type 4 echovirus infections: in one outbreak rash was frequently seen,[16] while in another, this was not one of the clinical features.[12] On a few occasions virus has been isolated from vesicular skin lesions associated with type 4 echovirus, and Coxsackie A5 infections.[1] Both Coxsackie A5 and A16 viruses induce a vesicular eruption of characteristic distribution, leading to the designation "hand, foot, and mouth disease."[25] In this syndrome, the oral lesions occur chiefly on the buccal mucosa and tongue, less frequently on the palate, gums and lips. The lesions on the extremities are interdigital, on the dorsum of the hands and feet, and involve palms and soles.

Rash has also been a prominent feature of certain echovirus infections, particularly those caused by types 9 and 16. In "Boston exanthem" (type 16) the eruption appears as fever and other systemic symptoms subside.[21] Echo 9 infections, epidemic in Europe and the U.S.A. during 1956-1959, were often accompanied by a dramatic eruption, most prominent and persistent on the face. As with most enterovirus rashes, the lesions were present chiefly in children under five years, and were seen in relatively few over 15 years.[26]

Herpangina; hand, foot and mouth disease and lymphonodular pharyngitis

The most distinctive disease induced by the Coxsackie A viruses is *herpangina*. This syndrome was reported first by Zahorsky in 1924 and his description of the clinical manifestations has not been surpassed. Herpangina is not often seen by internists, for it is primarily an infection of young children who present with fever and typical oral lesions, not more than 15 or 20, in the posterior pharynx and on the tonsillar pillars. These are tiny vesicles which go on to become punched out ulcers surrounded by bright red areolae. Other Coxsackie A syndromes include the previously mentioned hand, foot and mouth disease, and the recently described clinical entity, *acute lymphonodular pharyngitis*.[30] So far only Coxsackie A10 has been isolated from patients with this syndrome in which the diagnostic lesions are nonulcerating nodules in the posterior pharynx and occasionally on the conjunctivae.

Aseptic meningitis

Neurologic syndromes associated with enteroviruses cover the spectrum from mild aseptic meningitis to fatal encephalomyelitis. Whatever the clinical response, however, the pattern of virus excretion and the development of antibodies is similar (Chart 1). Aseptic meningitis, the commonest neurologic manifestation, has been associated with many different virus types both in epidemics and as probable etiologic agents in sporadic cases (Table 6). The types responsible for large epidemics have been relatively few: Coxsackie A7 and 9; Coxsackie B1-5; and echoviruses 4, 6 and 9. An etiologic diagnosis is made most readily by virus isolation from the stool or pharyngeal secretions. Spinal fluid is also a good source of virus when the infection is due to Coxsackie A or B or a number of echoviruses,[18] but the agent is rarely recovered from the spinal fluid in cases of poliomyelitis.[28] Diagnosis based on serologic tests alone—that is, by screening acute and convalescent sera to demonstrate an antibody rise against a specific enterovirus—is not often attempted because of the multiple serotypes (more than 60) which might be involved.

As with other enterovirus syndromes, more cases of aseptic meningitis are seen in children than in adults, but in some recent outbreaks as high as 50 per cent of patients have been adults.[15] This trend is significant, for the severity and duration of the clinical course tends to increase with age. Often, as in mumps meningitis, there is also a difference in the incidence of the disease in the two sexes, the ratio of cases in males to females being at least 2:1 in those under 20 years.[18,20] Over the age of 20, cases in women predominate, presumably because of their greater exposure to young children, the chief virus disseminators.

TABLE 5.—*Enterovirus Infections Associated with Rash*

Commonly	
	Echovirus 4, 9, 16
	Coxsackie A 9, 16
Occasionally	
	Echovirus 1-3, 5, 6, 11, 14, 18, 19
	Coxsackie A 2, 4, 5
	Coxsackie B 1, 3-5

There are few clinical features of aseptic meningitis which suggest the etiologic agent responsible. Some of the viruses are among those commonly associated with rash, such as Coxsackie A9 and ECHO-9, and this may be a helpful diagnostic point (Table 5). With ECHO-9 virus infections there is a tendency to unusually high spinal fluid cell counts, even up to several thousands, with 40 to 60 per cent or more polymorphonuclear cells persisting for a number of days.[10] If there is a petechial rash, as may occur in infections with ECHO-9, it may be difficult to distinguish between aseptic and meningococcal meningitis. The possibility of inadequately treated bacterial meningitis also comes up when the patient has received antimicrobial therapy which may have been sufficient to modify the clinical manifestations without having eradicated the agent. In general, however, the viral nature of the infection is indicated by the milder course, the normal or modestly elevated leukocyte count in peripheral blood, and the cerebral spinal fluid findings early in the illness: cell counts commonly in the range of 50 to 300 per cu mm with a predominance of lymphocytes, normal glucose levels and normal or slightly increased protein content.

Encephalomyelitis

It seems likely that any agent which can invade the central nervous system and induce aseptic meningitis may also under certain circumstances result in paralytic or encephalitic disease.[8,29] Some ECHO and Coxsackie viruses have already demonstrated their capacity to do this, and even to result in fatal infections, particularly in very young children. For the world as a whole, however, polioviruses still account for more than 95 per cent of cases of paralytic poliomyelitis. But as this disease has declined in the United States and elsewhere, it has become increasingly apparent that diseases indistinguishable from it clinically can result from infection with other enteroviruses. These agents have been recovered from spinal fluid and cord or brain of some of the fatal cases.[8] The pathologic findings are similar to those of poliovirus infections in type, although often with some differences in distribution in the central nervous system. Coxsackie A-7 virus has been more frequently associated with definite paralysis than have the other non-polio enteroviruses. It has caused outbreaks of aseptic meningitis, with a number of cases of paralysis in the U.S.S.R. and in Scotland,[6] and several fatal cases have been reported. Our Russian colleagues have been so impressed with the paralytogenic potential of Coxsackie A-7 virus that they have suggested that it be called Type IV poliovirus.[3]

Among the echoviruses, types 6 and 9 have been responsible for many cases of mild muscle weakness which persists for several months and then disappears. Residual paralysis or fatal disease has been rare with these two types as with echoviruses generally.[8]

Other clinical manifestations which have been reported as due to various enteroviruses include encephalitis and paralysis with sensory loss, diagnosed clinically as the Guillain-Barré syndrome,[8] and encephalomyocarditis in the neonatal period, which deserves special mention.

TABLE 6.—*Neurologic Disease Syndromes Associated with Enterovirus Infections*

Syndrome	*Associated Agents*
Aseptic meningitis	Poliovirus 1-3 Coxsackie A 2, 4-11, 16-18, 22-24 Coxsackie B 1-6 Echovirus 1-9, 11-14, 16-19, 20-25, 30, 31
Paralysis	Poliovirus *1**, *2*, *3* Coxsackie B *1*, *2*, *3*, *4*, *5* Coxsackie A *2*, *4*, *7*, *9* Echovirus *1*, 2, 4, *6*, *9*, *11*, 13, 16, *30*
Encephalitis	Coxsackie B *5* Coxsackie A 2, 4, 5, 6, 8, 9, 18 Echovirus *9*, 14, 19
Encephalomyocarditis (neonatal)	Coxsackie B *1*, *2*, *3*, *4*, *5*

*Types which have been associated with fatal illness or residual paralysis are in italics.

Encephalomyocarditis, myocarditis and pericarditis

The syndrome of encephalomyocarditis in newborns has been prominently associated with the Coxsackie B group of viruses. Newborn nursery epidemics have been reported in many parts of the world, always associated with a high mortality rate.[11,14] Virus has been recovered frequently from heart, brain and viscera. Because of the potential danger when Coxsackie B viruses are introduced on an obstetrical service, the woman who at the time of delivery has fever and other evidence of an acute viral infection—no matter how mild—is suspect, and should be isolated.

As to myocarditis and pericarditis in older children and adults, the Coxsackie B viruses have been implicated in some 15 reported cases, and there have been rare cases attributed to Coxsackie A viruses. Coxsackie B4 virus has been recovered from the pericardial fluid of a 13-year-old girl, the only fatal case recorded in a patient over two years of age.[27] In 14 others (aged 2½ to 36 years) with the characteristic clinical features, the diagnosis has been made on the basis of virus isolation from the feces and/or antibody rises. All of these patients recovered without apparent residual effect. There is at present no virologic evidence to link sporadic cases of chronic progressive myocarditis in children or adults to infection with Coxsackie viruses, although this possibility cannot be completely ruled out.

Pleurodynia (Epidemic myalgia; Bornholm disease)

Pleurodynia is not a common disease but it is one of the most typical manifestations of Coxsackie B virus infections. It usually occurs in epidemic form; sometimes there is an associated myocarditis or pericarditis or, more frequently, aseptic meningitis. Orchitis has been reported as a complication in some outbreaks,[31] and more rarely pneumonitis. In adults the characteristic onset is with sudden severe chest pain (devil's grip) similar to pleuritic pain, while in children abdominal pain is more frequent. In both, the problem is acute myositis involving chest, diaphragm and abdominal muscles. A few cases have been linked with echoviruses, but to date these are very rare and pleurodynia is essentially a Coxsackie B virus syndrome.

Acute respiratory illness

Only in the past few years has it been appreciated that enteroviruses are sometimes associated with respiratory illnesses.[13] Lennette and his colleagues established Coxsackie A21 as the etiologic agent in an epidemic of upper respiratory infections in a military population.[17] ECHO 11 and 20 have also been incriminated in naturally occurring infection, and ECHO 11 has induced the common cold in volunteers. Pneumonia and other lower respiratory tract disease are less common, but have been reported with Coxsackie B virus infections.

Enteritis-diarrheal disease

Finally, we come to what one might logically expect to be first—enteritis caused by enteroviruses. Paradoxically there is little firm evidence to implicate these agents except in a few epidemics, chiefly in infants, in which echoviruses type 14 and 18 were demonstrated to be the etiologic agents. There is a less definite association between diarrheal disease and other enteroviruses except perhaps in semi-tropical environments.[24] In the familiar clinical situation of acute gastroenteritis occurring as a family or institutional outbreak, frequent efforts to isolate enteroviruses have been fruitless. It appears that in general the currently known enteroviruses are not important causes of enteritis.

Comment

This brief review of a large and diverse subject has emphasized the similarities between the clinical manifestations caused by a number of different agents, and the impossibility of making a specific etiologic diagnosis except by laboratory means. Nevertheless, recognition of these syndromes and an appreciation of their diverse etiology should aid the clinician in dealing with acute febrile illnesses. Basically, the problem when one sees a patient with fever and other evidences of acute infection, is whether the infecting organism is bacterial or viral. On the basis of epidemiologic features—season of the year, age of the patient, prevalence of similar illnesses in the community—together with the particular clinical manifestations, an educated guess as to an enterovirus etiology is often possible. Recognition of the viral nature of such illnesses is of importance in terms of management, not because specific drugs are available (although the day is sure to come when they will be) but so that antibiotic agents and other antimicrobials will not be used unnecessarily. In this day of ever increasing incidence of iatrogenic drug-induced diseases, this consideration is a serious one.

With the virtual disappearance of poliomyelitis in the United States and other countries with a well vaccinated population, the other enteroviruses are assuming greater relative importance, particularly in the etiology of central nervous system disease. So far there is no evidence that these agents are becoming more widespread or more virulent as a result of the departure of wild polioviruses. But the appearance of "new" agents and the factors governing the epidemic rise and fall of both new and old enteroviruses are as poorly understood as ever. Changing epidemiologic patterns have been such a characteristic feature of poliomyelitis, it would be surprising if infections due to other enteroviruses did not also exhibit similar behavior. It seems safe to predict that these agents will have a lively future, and that "new" members and "new" clinical syndromes will be added, probably when we least expect them.

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Differential Renal Function Study

An Aid in Preoperative Evaluation of Hypertensive Patients

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■ *Non-occlusive ureteral catheters were placed bilaterally in the renal pelves of 30 patients known to have hypertension. Samples of urine were collected under conditions of normal hydration, of urea-PAH-saline diuresis and, in some cases, mannitol diuresis. The samples were analyzed for indications of impaired flow of blood to the kidneys. Aortograms were obtained in all cases.*

This placement of non-occlusive catheters up into the renal pelves was felt to have caused only minimal disturbance of renal function, and was not accompanied by ureteral edema with the concomitant complications caused by occlusive catheters. Under conditions of normal hydration, leakage was insignificant.

Of the 20 patients in whom urea-PAH-saline infusion revealed an ischemic pattern, 19 had an ischemic pattern under conditions of normal hydration. Since in the one exception an aortographic examination did not show a surgically reparable renal lesion, it may be inferred that the use of urea-PAH-saline diuresis is not essential in the preoperative evaluation of hypertensive renal disease.

Correlation of the results of differential renal function studies and aortographic findings was possible in 19 of the 30 patients. Lack of correlation in the remaining 11 patients emphasized the importance of obtaining both types of study.

Aortographic examination combined with differential renal function studies, using small ureteral catheters under conditions of normal hydration, should give the urologist a practical and yet accurate method of determining differential renal blood flow. If desired, further verification could be obtained by administering contrast medium and performing serial measurements of urine density.

WITH A BETTER UNDERSTANDING of renal physiology and improved techniques in vascular operations, surgical treatment of hypertension secondary to renal vascular disease has come to the fore. The results of treatment, however, have been variable, with success depending to a large extent on careful selection of patients through preoperative evaluation.

A surgically reparable lesion of the renal vasculature is best demonstrated visually by aortography. However, a lesion that is demonstrated aortographically is not necessarily a lesion that causes hypertension; the caliber of the renal artery must be decreased by 50 per cent before a de-

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crease in renal blood flow can be detected.[5] Thus, preoperative evaluation must also include tests that give some indication of the supply of blood to the kidneys.

The most practical means of evaluating renal blood flow is by measuring the physiological effects of its impairment. This is accomplished through tests of differential renal function. The procedure outlined by Stamey (1962)[5] is probably the most accurate of the differential renal function studies. It is based on sound physiological principles. The ischemic kidney is a water-reabsorbing kidney and the urea administered for the Stamey test potentiates this reabsorption. Determinations of urine volume reflect most sensitively the degree of reabsorption. As now performed, the Stamey test requires the use of unilateral or bilateral occlusive catheters placed part way up the ureters. Various complications of this test have been reported.[6]

The purposes of the present study were: (1) to determine if a satisfactory study could be carried out with catheters of less than occlusive size inserted to a level just above the ureteropelvic junction; (2) to determine if the administration of urea is necessary for the detection of renal impairment due to decreased renal blood flow; and (3) to correlate the results from the differential renal function studies with the aortographic findings in the same patients to see if both diagnostic methods are essential in the preoperative evaluation of these patients.

Materials and Methods

Samples of urine were obtained from 30 hypertensive patients under conditions of normal hydration, of ureapara-aminohippuric acid-saline diuresis, and, in some cases, mannitol diuresis. Aortograms, excretory urograms and occasionally radioisotope renograms and renal scintigrams had been taken in these patients.

A series of nine collections (18 unilateral specimens obtained from each patient through whistle-tipped catheters—No. 6F in males and No. 7F in females—placed just above the ureteropelvic junctions) were analyzed for volume, osmolarity, concentrations of electrolytes, creatinine, urea nitrogen, phosphate and para-aminohippuric acid (PAH). Also determined were differential phenolsulfonphthalein (PSP) excretion and concentration[6] as well as specific gravity of urine from each kidney following the intravenous administration of contrast medium.[1,2] All differential renal function studies were performed by the same person.

Differential Renal Function Tests

When the flow of blood to one kidney is impaired, excessive reabsorption of water by that kidney and increased concentration of excretory products in the urine from that kidney occur. These excretory products can be endogenous (such as potassium or creatinine) or exogenous (such as PAH, PSP dye, or any contrast medium similar to those used for excretory urography). In a "classic" case of renal artery stenosis (Figure 1) the findings on excretory urography are: (1) a smaller kidney, (2) delayed appearance of the dye, followed by (3) hyperconcentration of the dye, all on the involved side. It is impossible visually to measure accurately the degree of this concentration of contrast substance. However, an objective measurement of the concentration of

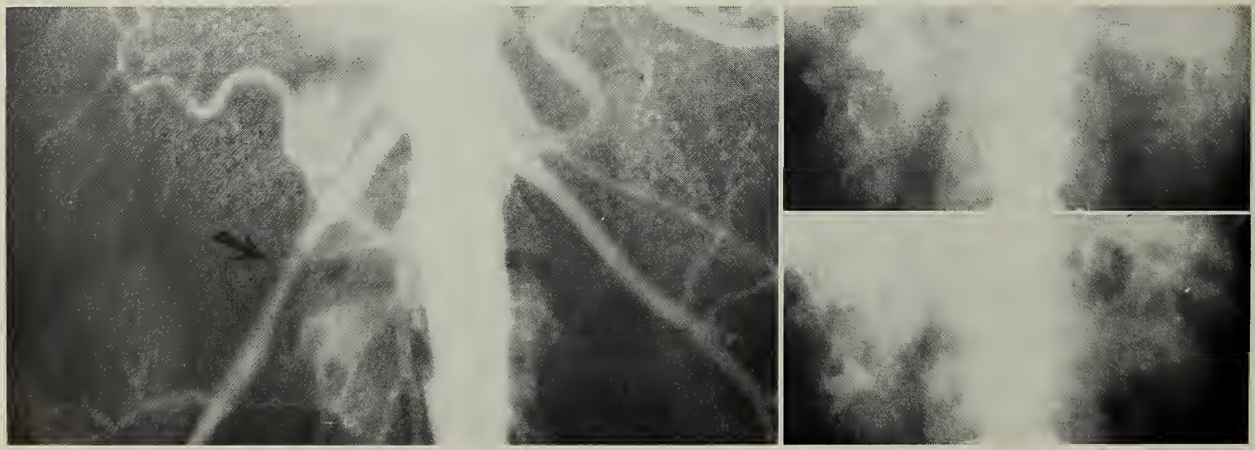

Figure 1.—*Left,* aortogram showing a stenotic area of the right renal artery. *Right,* excretory urogram demonstrates *(in the upper frame)* the smaller right kidney with delayed excretion of contrast substance. The 30-minute exposure *(lower frame)* is suggestive of hyperconcentration on the right side.

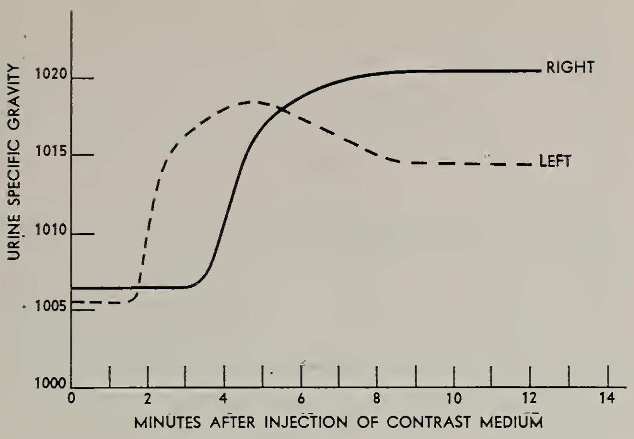

Chart 1.—Curves of urine gravity in a case of right renal artery stenosis. Note the delayed ability of concentration followed by hyperconcentration from the right kidney.

contrast substance can be obtained by measuring with a refractometer the specific gravity of samples of urine obtained simultaneously from both kidneys.[1,4] The measurements are charted for each kidney as shown in Chart 1. In the present study, the results of these measurements correlated well with the findings from other tests for determining impaired renal blood flow.

Of the various excretory products determined, creatinine concentration was the most reliable as an indicator of renal ischemia. The differences in concentration of urea nitrogen were less pronounced, and were probably secondary to the increased reabsorption of urea in the presence of decreased tubular flow of urine in the ischemic kidney.[3] The ratio of urea to creatinine might, therefore, be a useful adjunct in the preoperative evaluation of a patient with an ischemic kidney.

Determinations of phosphate followed the same pattern of increased concentration from the ischemic kidney, but to a lesser degree than the other substances. Sodium and chloride concentrations were unreliable tests under conditions of urea-PAH-saline diuresis.

Leakage around the catheters was almost nonexistent under conditions of normal hydration, and averaged approximately 6 per cent under urea or mannitol diuresis. Where small volumes allowed for complete flow without leakage, measurement of total excretion and concentration of PSP accurately demonstrated unilateral renal ischemia. No evidence of ureteral edema was encountered.

Urea-PAH-saline stimulation revealed an ischemic pattern in 20 patients. In 19 of them there was an ischemic pattern under conditions of normal hydration as well. In the one patient in whom urea diuresis revealed an ischemic pattern and the findings under normal hydration were essentially normal, there was no lesion apparent on aortographic examination. This suggests that urea diuresis is not necessary for detecting a surgically reparable lesion. Mannitol diuresis, in contrast to urea diuresis, decreased the differences between the two kidneys by diminishing the osmotic gradient in the medullary tissue.

Correlation of Aortograms and Renal Function Studies

In 14 of the 30 patients tested, an ischemic kidney was demonstrated both by aortographic examination and differential renal function studies (Table 1). In five patients, no ischemic pattern was detected nor was there visual evidence of a vascular lesion. However, in the remaining 11 patients, there was no correlation, and this lack of correlation should point up the importance of carrying out both types of diagnostic testing in order to plan a rational surgical approach.

From the evidence that we have at present, an aortographically demonstrable lesion that does not cause an ischemic pattern in function studies must

TABLE 1.—*A Comparison of the Results of the Test of Differential Renal Function with Findings on Aortographic Examination in a Series of 30 Patients with Hypertension*

	Number of Patients
I. Correlation of aortographic observations with function studies	
A. Lesion on aortogram and ischemic pattern in function study	14
B. No lesion on aortogram and no ischemic pattern in function study*	5
Total	19
II. Lack of correlation of aortographic observations with function studies	
A. Lesion on aortogram and no ischemic pattern in function study	3
B. No lesion on aortogram and ischemic pattern in function study	3
C. Lesion on aortogram on side opposite from that showing ischemic pattern in function study	2
D. No lesion on aortogram and questionable false positive ischemic pattern (pyelonephritis) in function study	3
Total	11

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*One of these patients showed an ischemic pattern under urea diuresis.

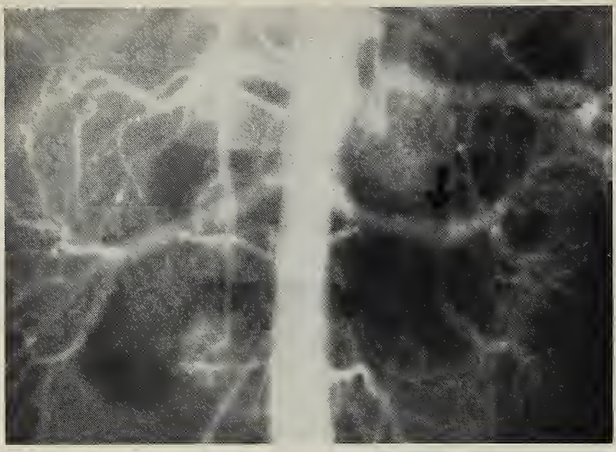

Figure 2.—Aortogram showing fibromuscular hyperplasia in the left renal artery. An ischemic pattern was found on function study from the right kidney.

be assumed to be insufficiently occlusive to cause a perceptible decrease in renal blood flow, and, therefore, is probably not responsible for the patient's hypertension. Where no lesion is seen grossly on an aortogram, and yet an ischemic pattern is noted in function studies, multiple segmental or branch lesions may be limiting the overall decreased vascular supply to the kidney. It is unlikely that patients of this order should be treated surgically.

The situation that best points out the importance of performing both types of study is one where an ischemic pattern is noted in the kidney opposite a kidney in which a lesion has been noted aortographically. Figure 2 shows the aortogram of a ten-year-old boy who had had severe hypertension from the age of three months. The obvious lesion of the left renal artery was felt to be one of fibromuscular hyperplasia; the vasculature to the right kidney was grossly normal. Yet from the right kidney, an ischemic pattern was obtained.

In contrast to the excessive water-reabsorbing pattern characteristic of renal ischemia, a pyelonephritic kidney may excrete a greater fraction of its filtered water than the contralateral kidney. This may lead to possible false interpretation of an ischemic pattern for the normal kidney. Fortunately, a history of recurrent infections or a urographic examination will usually clarify the situation.

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Correction

Table 2 which appeared in the article, "Rubella and the Rubella Syndrome—New Epidemiologic and Virologic Observations," by Dorothy M. Horstmann, M.D., in the June issue of California Medicine contained erroneous entries. The corrected version follows:

TABLE 2.—*Virus Isolation from Fetal Tissue Obtained at Induced Abortion*

Weeks After Maternal Rubella	*Virus Isolations*	
	Number Positive	*Number Tested*
< 2	2	3
2 - 3	4	5
4 - 5	2	4
6 - 7	1	3
8 - 9	1	1
> 9	0	2
Total isolations	10 (56%)	18

Tests for Syphilis

The Increasing Incidence of Biologic False Positive Reactions as Measured by Treponema Pallidum Immobilization

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■ *Analysis of data obtained in 25,787 Treponema pallidum immobilization tests in a ten-year period showed an increase in the incidence of biologic false positive (BFP) reactions for syphilis, and a decrease in the incidence of reactive TPI tests. The percentage of BFP tests increased from 54.2 per cent in 1953 to 70.7 per cent in 1962.*

Reaction to a standard serologic test for syphilis (STS) indicates only that the patient may have syphilis. A subsequent non-reactive TPI test remains the best procedure for ruling out a diagnosis of syphilis. Thus the clinician should be made more aware of the fact that a biologic false positive reaction strongly implies the existence of another disease, the cause of which should be investigated.

In 1949, the specific *Treponema pallidum* immobilization test was developed by Nelson and Mayer.[6] This procedure makes possible the accurate differentiation of biologic false positive (BFP) reactions from reactions caused by syphilis. It is now known that numerous diseases such as the collagen diseases, certain neoplastic diseases and brucellosis, and physiologic states such as pregnancy and narcotic addiction, may produce biologic false positive reactions.[5,3,2,4]

Materials and Methods

The *Treponema pallidum* immobilization test was performed according to the method of Boak and Miller.[1] During the decade (1953-1962) 25,787 specimens of serum obtained from patients with a history of having one or more positive reactions to serologic tests for syphilis (STS) were tested.

Results

For the ten-year period under investigation the incidence of BFP reactors gradually increased from 54.2 per cent to 70.7 per cent. The per cent of reactive TPI tests fluctuated from year to year, with a reduction of 13.9 per cent between the years 1953 and 1962. The results obtained from our study and the statistical analysis are summarized in Table 1. Statistical interpretation of these data is presented in Figures 1 and 2.

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TABLE 1.—*Regression of Biologic False Positive Reactions for Syphilis (1953-1962)*

Year	*Number of Sera Tested*	*Per Cent Non-Reactive TPI (BFP)*		*Per Cent Reactive TPI*		*Per Cent Doubtful TPI*
		Actual	*Regression*	*Actual*	*Regression*	
1953	1,188	54.20	54.4	42.17	43.4	3.61
1954	1,501	52.09	55.8	45.36	42.0	2.53
1955	1,880	60.15	57.3	37.02	40.6	2.81
1956	2,187	59.71	58.7	38.95	39.2	1.32
1957	2,783	57.20	60.1	41.10	37.7	1.68
1958	2,845	61.19	61.6	37.04	36.3	1.75
1959	3,743	63.50	63.0	33.50	34.9	2.99
1960	3,464	62.26	64.4	34.69	33.4	3.03
1961	3,073	67.29	65.8	32.05	32.0	0.65
1962	3,123	70.70	67.3	28.24	30.6	1.05
1963	....	....	68.7	....	29.1	......
1964	....	....	70.1	....	27.7	......
1965	....	....	71.6	....	26.3	......
1966	....	....	73.0	....	24.8	......

The trends observed are statistically significant. Inasmuch as definite trends do exist, the percentages have been projected to 1966. If the trend of the past ten years continues, the projected value for non-reactive TPI tests will be 73 per cent.

Discussion

The increasing incidence of BFP reactions during the ten-year period 1953-1962 has important implications. Although many investigators have pointed to the increase in the incidence of syphilis since 1957, little attention has been paid to the growing problems associated with those individuals who react to the lipoidal antigens yet do not have syphilis. Clinicians should be aware of the importance of diagnostic follow-up of such patients. Literature is replete with examples of not only acute diseases causing these reactions but also chronic illness. Perhaps the most important consideration in this respect is the fact that many of the BFP reactors had no evidence of another dis-

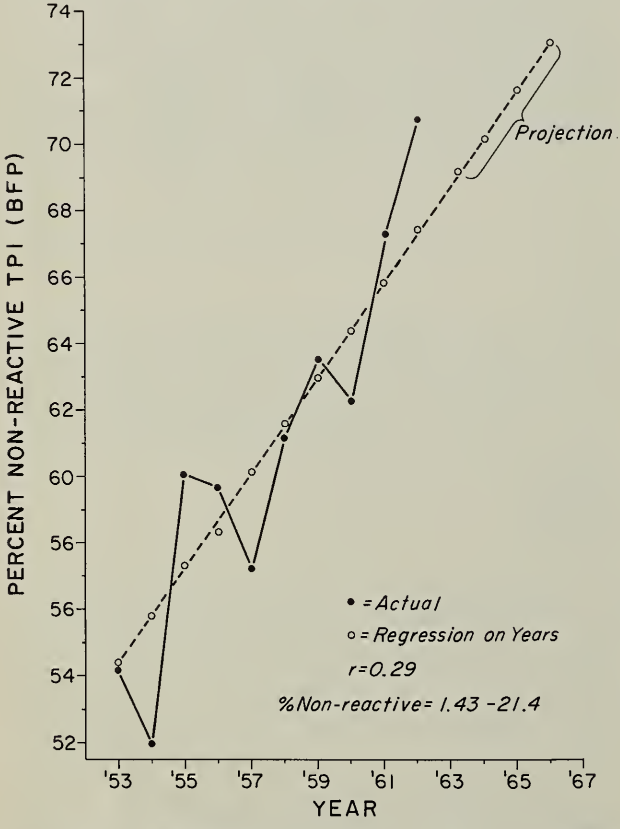

Chart 1.—Regression with time (in years) of biologic false positive reactions for syphilis (1953-62).

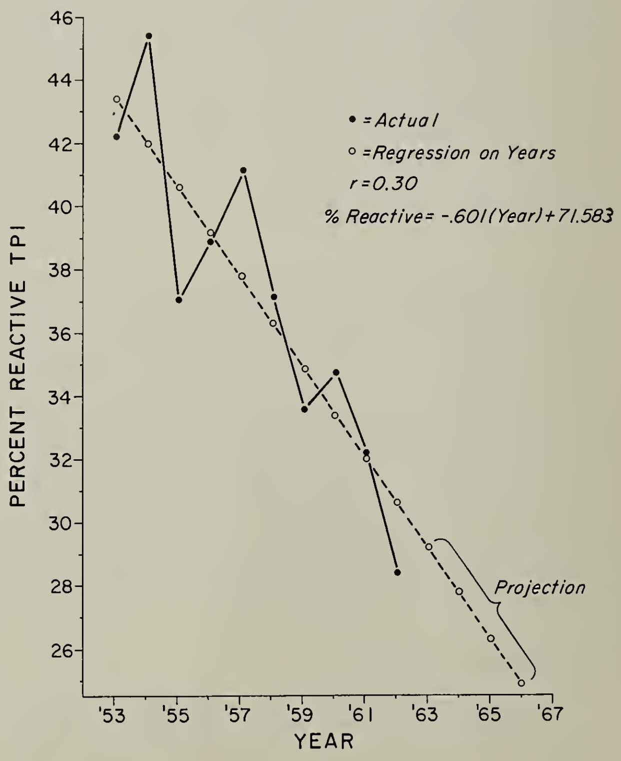

Chart 2.—Regression with time (in years) of reactive Treponema pallidum immobilization (TPI) tests for syphilis.

ease at the time the BFP was detected. It is of paramount importance that such persons be observed every six months, particularly in view of the finding by Moore and Mohr[5] that this can be indicative of an underlying disease process that may fulminate later.

A second important consideration is the fact that patients with a reactive STS and a reactive TPI test may have latent syphilis in combination with other diseases.[3] It is likely that the Wassermann-fast patient may fall into this category.

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ACKNOWLEDGMENT

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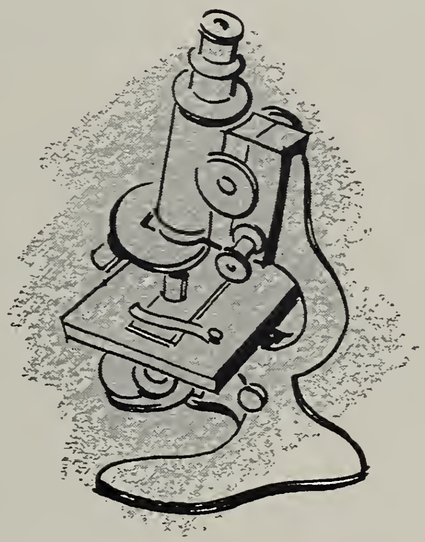

Infraclavicular Subclavian Angiography By Percutaneous Puncture

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■ *Successful visualization of the extracranial circulation and posterior basilar-vertebral complex was accomplished with a modified technique for direct percutaneous infraclavicular puncture of the subclavian artery.*

The advantage of the described method over other methods relates to the simplicity and safety of the technique. The advantages outweigh the not serious complications which may be encountered.

ANGIOGRAPHIC VISUALIZATION of the vertebral basilar complex is often necessary in suspected vascular occlusive disease, in subarachnoid hemorrhages and in vascular insufficiency due to cervical spondylosis or cervical trauma. For these studies, different approaches have been used in the past.[6,9,10] The limitations of such methods for use as routine procedures are the excessive time required and the frequent complications.

Subclavian injection appeared to be the most logical method of demonstrating the origin of the vertebral artery and of avoiding the hazards of vertebral artery puncture. Since supraclavicular approach for the subclavian puncture, described by many investigators (Baker,[2] Barbieri and Verdecchia,[3] Crawford and coworkers,[4] Shimidzu[9] and others) often produces pneumothorax and hemomediastinum, a more convenient and less hazardous modification of the procedure was sought. Puncture of the third portion of the subclavian artery infraclavicularly rather than of the first portion of the vessel seems to greatly minimize possible complications.

We have used this site in more than eighty cases. Our modified technique assures consistently a successful puncture of the subclavian artery without having a serious complication.

Review of Infraclavicular Technique

Pouyanne and coworkers (1960)[7] were the first to describe the subclavicular approach. When the subclavian artery is not palpable they seek for a point which, upon compression, will occlude the pulsation of the radial artery, and they redirect the needle to that target. Amplatz and Harner (1962)[1] suggested that the insertion of the needle be made one finger width lateral to the midclavicular line and about one finger width below a line passing transversely through the jugular notch. Weibel and Fields (1963)[11] introduced the needle subclavicularly at the point of the junction of the internal and middle third of the clavicle. Ray (1963)[8] used a landmark initially located by halving the distance between the sternal notch and acromial tip of the clavicle. The needle was

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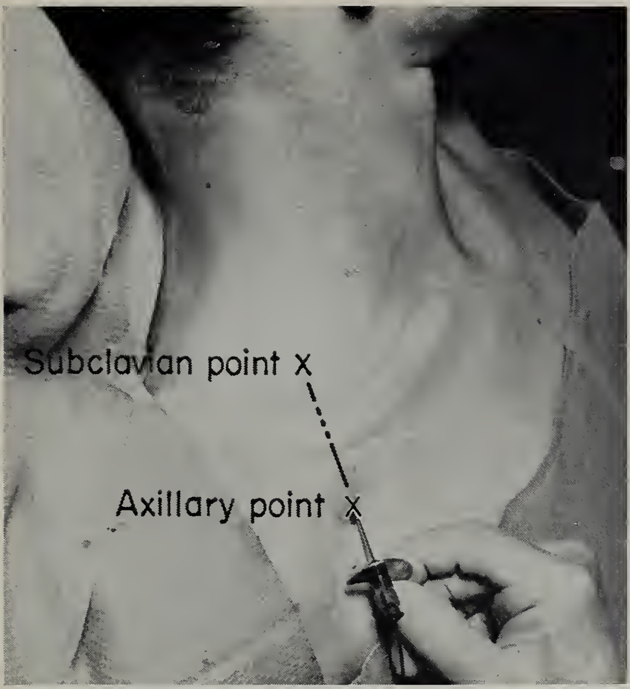

Figure 1.—The picture illustrates the orientation of the needle in the subclavian artery. Infraclavicularly the needle is directed along the line traced between the axillary point (Mohrenheim's triangle) and the subclavian point.

inserted subclavicularly in an ascending direction aiming toward the subclavian triangle formed by the scalenus anticus, the subclavian artery and the first rib. The needle was guided toward the scalenus anticus muscle itself or even more medially.

Technique

The patient is given 65 to 130 mg (1 to 2 grains) of sodium luminal one hour before the test. On the x-ray table a large rubber sponge or small pillow is placed between his shoulder blades helping to hyperextend both shoulders. The arms are gently pulled down or are placed in abduction, whichever is better.

The landmarks used to identify the site of the puncture are the subclavian artery in the subclavian triangle and the axillary artery in the delto-pectoral space (Mohrenheim's triangle*). The line between these two points will orient the insertion of the needle (Figure 1). Approximately 4 ml of 1 per cent procaine hydrochloride is injected one inch below the clavicle at the level of the palpable axillary artery. A Cournand-Grino needle is introduced at the point after a bore-hole on the skin is made with an 18 gauge needle, and is directed to penetrate the third portion of the subclavian artery (Figure 2) in the supraclavicular fossae. The likelihood that the target vessel will be punctured properly is enhanced by following these guides, since the needle so oriented will encounter the vessel in its long axis. The penetration of the vessel is confirmed when the subclavian artery pulse disappears or decreases as the result of compression by the needle. At times the first portion of the axillary artery will be penetrated (Figure 2). A rather vigorous blood flow is obtained when the inner needle is removed.

Care should be taken to prevent injury to the median nerve running in front of the third portion of the axillary artery. In this region the lateral and medial cords of the brachial plexus join to form the median nerve at the level of the teres major muscle. If the needle is directed too low, it may injure the nerves. When approaching the axillary artery area, the needle should not be directed too far medially because of the danger of penetrating the pleura.

If subclavian pulsations are weak or absent, an intravenous injection of metaraminol (Aramine®) 1 to 3 mg is given to elevate the blood pressure. This adjunct greatly facilitates puncturing the artery. The opposite subclavian artery may be punctured in the same manner.

A spot film is taken after injection of 3 ml of contrast medium (Hypaque®). This film will help to evaluate the x-ray penetration; to visualize the position of the needle in relationship to the wall of the artery, and to detect any faulty injection.

A series of anterior-posterior x-ray films, centered to include both sides of the neck, are taken 0.5 per second apart, and followed by an anterior-posterior intracerebral angiogram, made either from the right or the left side. Lateral views including both neck and head are then taken. Four to five exposures are made for visualizing the neck and eight to ten for demonstrating the intracranial circulation. A blood pressure cuff previously placed on the arms is inflated to 180 mm of water immediately before each injection. The injection is made rapidly by hand pressure, exposures being made when half of contrast material has been introduced for visualizing neck vessels and when injection is complete for head views.

At the conclusion of the study, the needles are withdrawn and the site of the punctures compressed for three minutes.

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*From Gray's "Anatomy"[5]: The Mohrenheim's triangle is the interval between the adjacent borders of the Deltoideus and Pectoralis major.

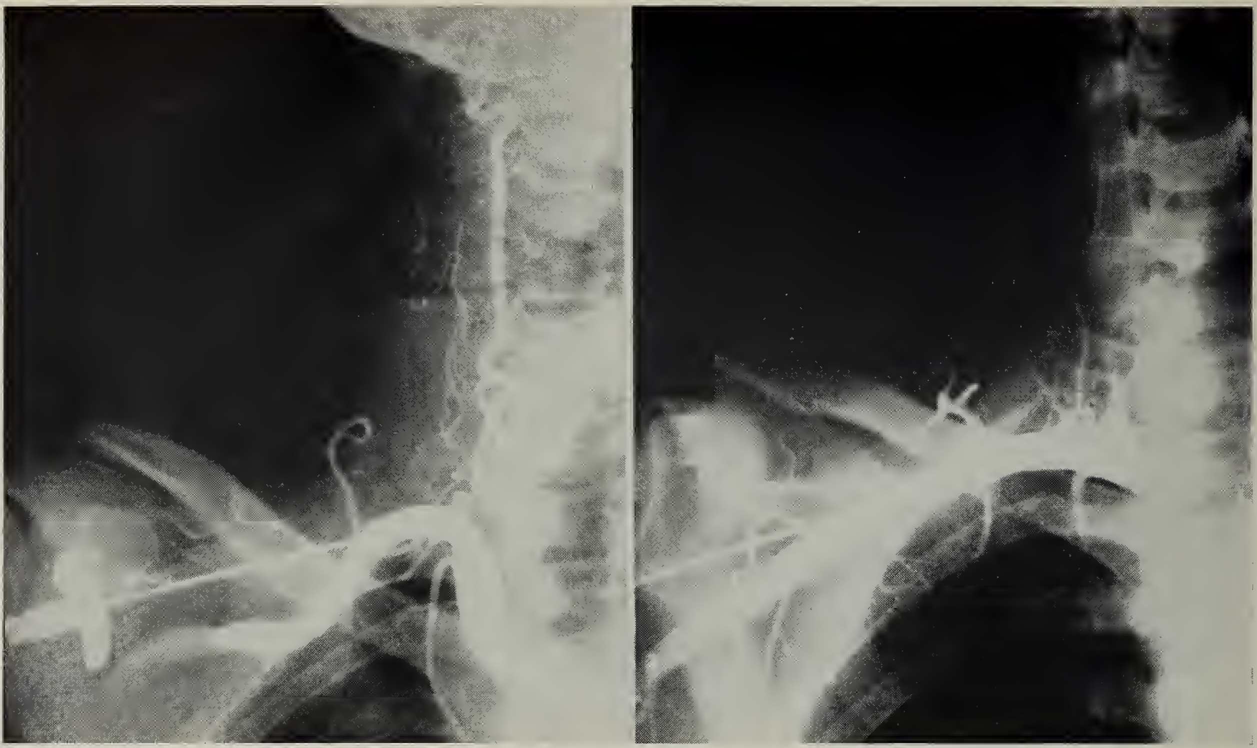

Figure 2.—The angiogram at the left shows that the needle is located in the third portion of the subclavian artery. In another study, right, the needle has punctured the first portion of the axillary artery.

Results

Patients were selected for subclavian angiography because of symptoms suggesting arteriosclerotic ischemia of the brain. Severe diffuse arteriosclerosis, unbalanced cardio-pulmonary insufficiency and active myocardial infarction were considered to be relative contraindications for the studies. Age was not a limitation, but the eldest patient studied was 71 years of age.

Both the subclavian and the vertebral arteries (as in Figure 3) were well demonstrated in every instance. The basilar artery and the posterior cerebral arteries were excellently visualized (see Figure 4). The right carotid was seen inconsistently and approximately 0.5 to 0.7 of a second after the vertebral artery came into view. Such visualization made it possible to demonstrate atheromatous plaques at the bifurcation of the carotid artery in the neck. The intracerebral visualization of the carotid system resulting from subclavian injection on the right side lacked good contrast at times, but angiograms so obtained were diagnostic in the majority of cases. Subclavian injection on the left side never caused such visualization. The lack of adequate outline of the right carotid artery may have something to do with the position of the needle in the subclavian artery, particularly when the injection is impeded by location of the needle orifice against the posterior wall of the vessel. When this occurs the needle must be withdrawn about 3 mm away from the intima into the lumen of the artery. This maneuver will also prevent a subadventitial or subintimal injection. The scout film originally taken will reveal the need for this modification.

As the left common carotid artery was never demonstrated with left injection of the subclavian vessel, percutaneous puncture of this vessel was always done to complete the study of the four vessels.

With this method, the head and neck can be turned without fear of dislodging the needle. Direct trauma to the vertebral artery is prevented, and the hazards of vertebral artery spasm due to direct puncture are greatly minimized. Furthermore, visualization of posterior fossa vessels is as satisfactory by this method as in direct vertebral injection.

Complications

In five of eighty cases, we were unable to puncture the subclavian artery. One of the patients had an acute clavicle angle and the other four were obese. Subadventitial extravasation (Figure 5) of the contrast medium occurred in three cases. It caused little discomfort to the patient. A

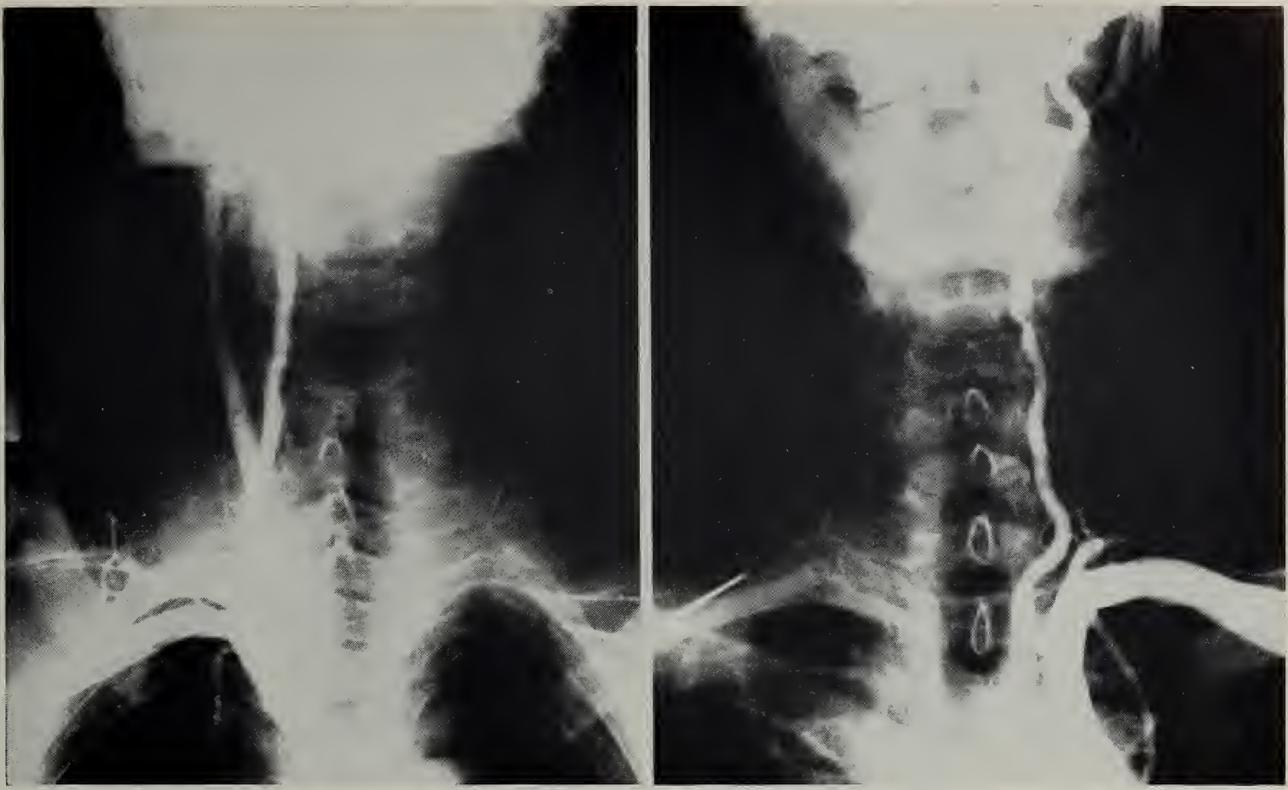

Figure 3.—These neck views visualize the extracranial circulation. Injections have been made bilaterally: In the film at the left, the right subclavian, the vertebral and the common carotid arteries are well visualized. An atheromatous plaque is present in the carotid bifurcation. *Right,* the left subclavian injection visualizes the subclavian and the vertebral arteries. Atherosclerotic changes are seen in the latter artery.

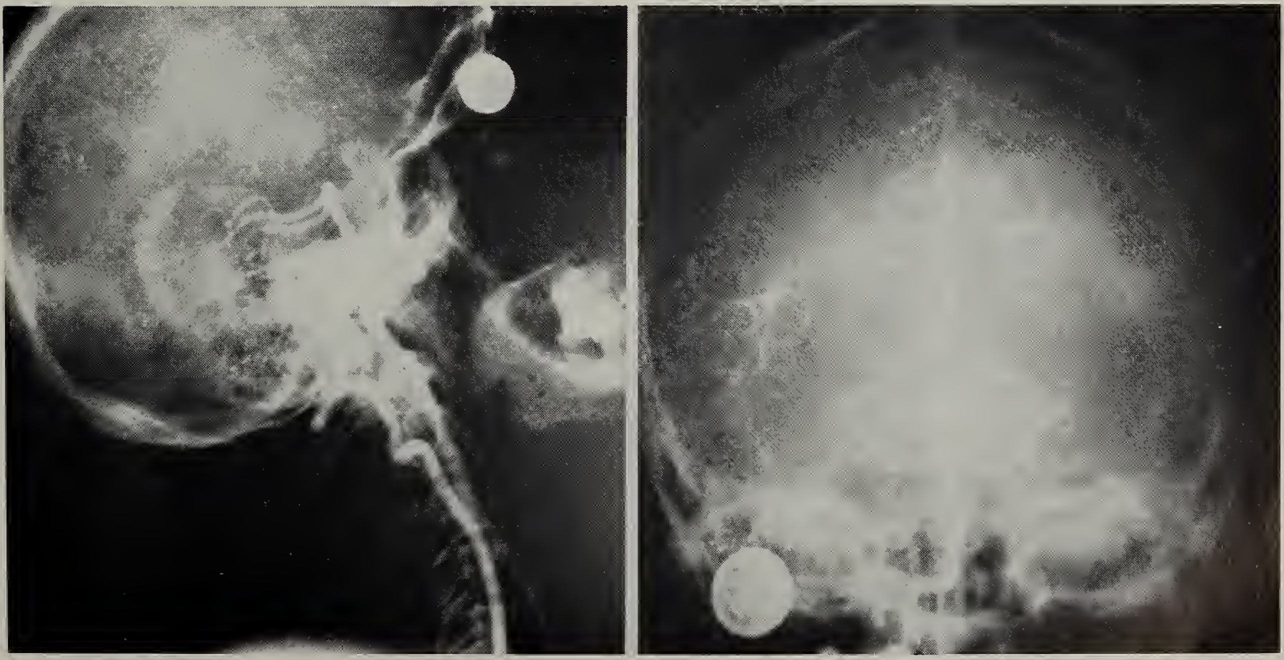

Figure 4.—*Left,* Lateral view of the neck and skull following subclavian injection, shows excellent visualization of the intracranial circulation. *Right,* Anteroposterior view demonstrates all branches in the posterior circulation. Note the middle cerebral artery, visualization on both sides.

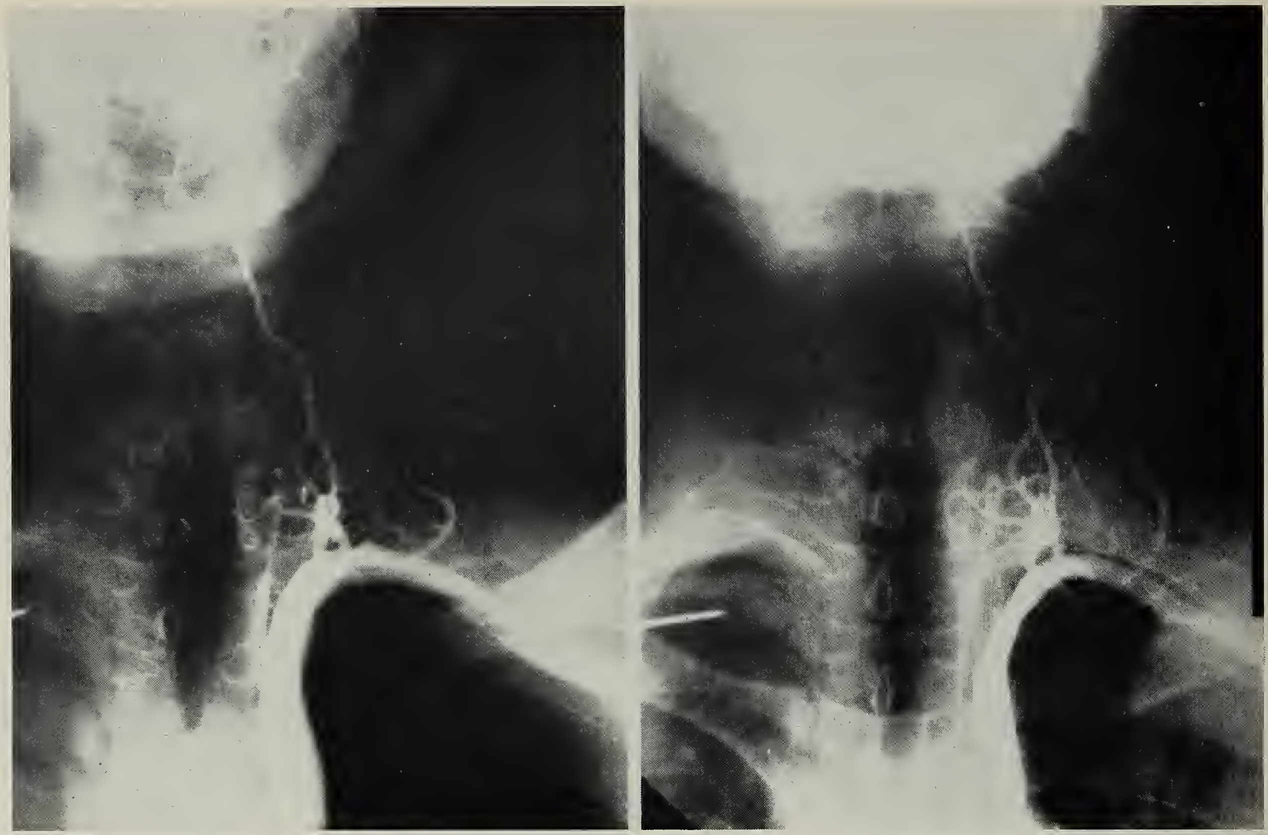

Figure 5.—*Left,* the angiogram shows faulty subadventitial injection extending downward to the origin of the subclavian artery. *Right,* following repositioning of the needle in the same patient, a narrow lumen of the vessel is demonstrated. The patient was found to have a complete occlusion of proximal two thirds of the vertebral artery. There was a well developed collateral circulation present, especially through the ascending and the costo-cervical branches as well as through the branches of the external carotid artery.

successful angiogram was obtained immediately after readjustment of the needle (Figure 5). No trace of the extramural Hypaque® was observed in repeat films taken a few minutes later.

In one patient with atheromatous plaque at the origin of the left vertebral artery, injection caused severe spasm of the vessel. This complication provoked a return of dysarthric symptoms which had been among the early and recurring complaints of this patient. A dilute solution of papaverine (30 mg) was injected slowly in the opposite subclavian artery that had been shown to be patent. The left subclavian artery was then revisualized, demonstrating relief of the vertebral spasm. The patient had recovered from dysarthria.

None of the patients studied complained of brachial plexus or peripheral nerve disturbances.

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ADDENDUM: Since the submission of this manuscript, the infraclavicular subclavian approach has been used in an additional 90 cases at the Long Beach Veterans Administration Hospital. This technique is now employed routinely by the staff and residents of our Neurosurgical Section. A single case of mild pneumothorax has occurred with no significant consequence. There have been no other complications in this group of cases.

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Ischemic Heart Disease

Use of Serum Enzyme Determinations in Diagnosis

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■ *The world literature since 1962 gives further substantiation of the usefulness of serologic measurement of glutamic-oxalacetic transaminase (GOT) activity and lactic dehydrogenase (LDH) activity in the diagnosis of myocardial infarction. LDH has not been found superior to GOT. The isoenzymes of LDH are now creating more and more interest because of their specificity for damage in various organs. This specificity, however, is not fully established.*

So MANY AND SO RAPID are the developments in the use of enzymes in the diagnosis of ischemic heart disease that constant review is needed to keep abreast of the advancing knowledge. This review will cover only the aspects of serologic diagnosis of ischemic heart disease which relate to the world literature during the year 1963.

Serum enzymes which have found diagnostic application can be divided into two groups: In the first group are those enzymes which have a specific relationship to the tissue of origin and which have a high degree of specificity for a particular disease or group of diseases—for example, serum amylase or serum acid phosphatase. The enzymes in the second group are involved in important intermediary metabolic sequences and are found in many tissues in varying concentrations—the transaminases, for example. Damage to such tissues leads to the passage of these enzymes into the circulation regardless of the organ of origin but in different amounts for each enzyme present. The time sequence of release of a particular enzyme in a particular organ furnishes information which is becoming more and more valuable in the diagnosis of disease.

White[18] pointed out some of the enigmas which still exist in the comparison of multiple serum enzyme levels. In studying patients with myocardial infarction he found a high serum lactic dehydrogenase (LDH) but a normal serum isocitric dehydrogenase (ICD) although the myocardium is rich in both enzymes. For elevations to occur, the equilibrium between the rate of enzyme elimination and the rate of entry from the blood must be disturbed; but there is no explanation of why certain enzymes do not increase when their tissue of origin is damaged. Such explanation must await better understanding of change of permeability of cells to enzyme content.

Wright and Warburton[70] stated that in 6 of 500 cases of acute myocardial infarction, glutamic-oxalacetic transaminase (GOT) and LDH were not elevated until 36 hours after onset. All these patients had very low blood pressures and the authors conjectured that hypotension may delay the rise. Sibley,[54] in a study of serum aldolase levels, pointed out that many questions concerning the basic physiology of serum enzymes still remain unanswered, among them the sources of abnormal enzymes in serum, how enzymes are eliminated from the blood, how normal levels are main-

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tained, and the like. It has also been demonstrated that although excess liberation of an enzyme into the blood is usually the result of tissue injury, liberation may also occur without histological evidence of cellular destruction. Many other investigators are seeking to answer some of these questions.[8] Experimental myocardial infarction by several methods is being used to study the mechanism of enzyme liberation in injured tissue.*

In the diagnosis of myocardial infarction, many enzymes have been studied and reported to have value: glutamic-oxalacetic transaminase,† lactic dehydrogenase (LDH),‡ aldolase (ALD),[39,54] glutamic dehydrogenase (GDH), malic dehydrogenase (MDH),[62] hexose isomerase (HSI), succinic dehydrogenase (SUC), acid phosphatase (ACP), hexose kinase,[39] glucose 6-phosphate dehydrogenase (G6PDH), isocitrate dehydrogenase (ICDH), creatine phosphokinase (CPK),[10,14,21,27] and serum alpha-hydroxybutyric dehydrogenase (HBD).[13,27,31,47] Many other enzymes are also being reported as useful: free ribonucleotides,[26] tripeptidase,[46] serum phosphocreatine kinase,[18,49,55,56] and histamine.[59]

Accuracy of GOT and LDH

Of these GOT and LDH have been most useful. The literature has been summarized through 1962[1] with the following results: For GOT in 2,227 cases, accepting the clinical criteria for myocardial infarction, there was elevation in 2,148 cases, or 97 per cent correlation. In 142 autopsy cases GOT was elevated in 137. For LDH in 477 clinically proven cases there was correlation in 450 or 95 per cent.

Recently, Meyers and coworkers[35] reviewed 157 cases of myocardial infarction confirmed by autopsy and compared serum GOT activity rise with electrocardiographic alteration. Increased serum GOT activity was found in 97.3 per cent and diagnostic electrocardiographic changes in 81.5 per cent.

Significant rises in canine experimental pericarditis and pulmonary infarction has also been established.[1] Karmen and coworkers showed the higher GOT activity of human cardiac tissue as compared with the relatively lower activity of an equivalent weight of serum.[1]

Spicka and Kralova[57] investigated the GOT:GPT ratio in acute myocardial infarction. In 85 per cent of cases the ratio was higher than 1.5:1 but in 38 per cent of cases it was less than 2:1. The results indicated that a high ratio of 2:1 cannot always be expected even in uncomplicated cases and thus the ratio may have limited value in the differential diagnosis of myocardial infarction.

Lactic Dehydrogenase

As has already been mentioned, the serum LDH activity has also been found reliably elevated in the presence of myocardial infarction.[71] Usually, LDH activity appears and reaches its peak later than does GOT activity. It is particularly useful where the patient is seen late, since it tends to remain elevated several days longer than does GOT. But these temporal relations may vary. Opinions differ as to the relative value of the two enzyme tests. Some investigators have concluded (and others have agreed) that if LDH is not elevated, the diagnosis of myocardial infarction can be excluded. However, Wroblewski stated that LDH changes have not been found to be any more reliable or helpful than serum GOT alterations.[71]

Isoenzymes of LDH

Despite the usefulness of serum enzymes in diagnosing myocardial infarction, there are many situations in which the diagnosis may be confused because of their non-specificity. Thoracic pain in association with a rise in serum enzyme activity is not specific for myocardial infarction, with or without electrocardiographic changes, fever, leukocytosis or an increase in the sedimentation rate. All these changes may be seen in severe pericarditis, large pulmonary infarcts, myocarditis, dissecting aneurysm, pancreatitis, biliary tract disease, trauma to the chest and heart including surgical operations and strenuous physical exercise. Then there are enzyme changes in conditions which often accompany or complicate myocardial infarction. Such rises are found in congestive heart failure, shock, arrhythmias, infarctions of the kidney, diseases of the muscle, liver disorders, alcoholism, central nervous system diseases, tumors of the heart, neoplasms and the use of various drugs.

Such non-specificity promises to be lessened by the use of isoenzymes which have much higher organ specificity, particularly the isoenzymes of LDH.* This enzyme comprises five electrophoretically separable isoenzymes having the same substrate specificity but dissimilar mobility speeds due to differences in amino-acid composition. Techniques have been devised which permit separation of these isoenzymes by taking advantage of their different physical characteristics, such as heat stability. Human lactic dehydrogenase consists of five distinct components having a characteristic distribution.[71]

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*Reference Nos. 15, 18, 24, 33, 37, 44.

†Reference Nos. 7, 9, 20, 25, 30, 32, 40, 41, 42, 60, 61, 63, 64.

‡Reference Nos. 5, 6, 11, 12, 23, 29, 34, 38, 43, 51, 58, 69, 71, 73.

The fastest moving fraction lies between albumin and alpha$_1$ (LDH$_5$); the second on the fastest part of the alpha$_1$ (LDH$_4$); the third between beta$_1$ and beta$_2$ globulin (LDH$_3$); the fourth on the gamma-globulin fraction (LDH$_2$); and the fifth on the slowest part of the gamma-globulin (LDH$_1$). Tissues with a high aerobic metabolism, like cardiac muscle, have a high content of isoenzymes which move fastest in the electrophoretic field (LDH$_4$ and LDH$_5$). The slowest isoenzyme (LDH$_1$) is found in greatest concentration in the liver.†

Since heart muscle contains no LDH$_1$ and liver is poor in LDH$_5$, liver disorders can be distinguished from heart disorders by fractionation of the isoenzymes. The intermediately moving substances, LDH$_2$, LDH$_3$, and LDH$_4$ are usually highest in tumors. Zondag[73] confirmed these patterns in over 4,000 determinations.

Serum or plasma of humans contains all five isoenzymes, the concentrations diminishing in the order: LDH$_4$, LDH$_5$, LDH$_3$, LDH$_2$, and LDH$_1$. Samples should not be stored in the frozen state or LDH may be inactivated. Myocardial infarction is characterized by elevations of LDH$_4$ and LDH$_5$. LDH$_5$ rises higher than LDH$_4$. Such changes are claimed to be more specific of myocardial infarction than LDH unfractionated, GOT, ALD, ACP, MDH or SUC.

The importance of this field is attested by a symposium which was organized by the University of Ghent and the Belgian Society for Clinical Chemistry. It was called "Multiple Molecular Forms of Enzymes" and was held in Ghent in April of 1963. The purpose of the meeting was to explore the clinical uses of isoenzymes.[67] Evidence was adduced that isoenzymes like LDH$_1$ and LDH$_5$ are composed of at least four sub-units, and several methods of enzyme separation were discussed: electrophoresis and elution, such as cellulose acetate electrophoresis, the tetrazolium procedure, column chromatography, activity measured by 2-Ketobutyrate and heat separation, among other methods. Amelung[2] advocated the cellulose acetate absorption method. Wright and Warburton[70] recommended the chloroform method for differentiating cardiac isoenzymes from other serum lactic dehydrogenases. All the isoenzymes, apart from heart muscle LDH, are decidedly inhibited.

Vesell,[65] a pioneer in the field, warned against the specific diagnostic value of LDH isoenzyme tests, because patterns of similar character can be found in several disease states. Shock, in particular, may liberate LDH from many tissues and thus have a distorting effect.

In 43 patients with hypotension and the clinical features of shock caused by hemorrhage, infection or vascular obstruction and without evidence of cardiac or hepatic disease, elevation of GOT occurred in 70 per cent, LDH in 52 per cent, and GPT in 37 per cent. The presence of myocardial infarction under such circumstances would not be substantiated by such measurements.[52]

Dubach and coworkers[11,12] used the heat separation technique for the diagnosis of myocardial infarction and its distinction from pulmonary infarction where there is very little elevation of LDH$_4$ and LDH$_5$.

Batsakis[5] preferred two methods of separation: one which uses the heat-stable and heat-labile properties of the isoenzymes, and the other which utilizes their relative activities in catalyzing the reduction of pyruvate and alpha-oxobutyrate. The component that is active against alpha-oxobutyrate has been designated as "alpha-hydroxybutyrate dehydrogenase" (HBD), and its colorimetric measurement represents a chemical differentiation of the cardiac enzymes in serum. Elliott and Wilkinson[13] considered this to be the best test for the diagnosis of myocardial infarction. From observation of 200 cases Batsakis[5] concluded that HBD levels remain elevated longer than GOT and LDH (10 to 14 days) and will help greatly in distinguishing myocardial injury when other organ systems are also involved.

It appears that plasma or serum of patients with myocardial infarction, including subendocardial infarction, show changes in isoenzymes of LDH which are highly characteristic. However, the changes are not specific since similar changes have been observed in shock states, carcinoma of the stomach, hypothyroidism and pernicious anemia. These changes are more specific than any other enzyme measurements and are particularly useful when other organs are involved, especially liver disorders. Moreover, the rise in LDH_5 may occur as early as one hour after infarction and may last five to ten days longer than total enzyme elevation. Wroblewski[71] claimed that in subendocardial infarction LDH_5 may be elevated when GOT and other enzymes remain normal. The heat stability test is relatively simple whereas the electrophoretic techniques are tedious and require special equipment.

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*Reference Nos. 5, 11, 12, 58, 69, 71, 73.

†It must be borne in mind that in much of the literature the isoenzymes are numbered in the opposite direction, so that LDH$_1$ becomes LDH$_5$ and vice versa.

Other Enzyme Tests

Konttinen and Halonen[27] compared CPK and HBD activities with those of GOT and LDH in 34 clinically diagnosed myocardial infarctions. They found the most definite rise in HBD activity and this activity persisted longer than that of the other enzymes studied. CPK averaged only three days before returning to normal levels. Moreover, CPK determinations are technically more laborious. Measurement of CPK activity is useful in the appraisal of disease states complicated by liver involvement, since it does not rise in liver disease.

Many other enzyme alterations have been described in acute myocardial infarction. Nagano and Hochrein[39] have reported on aldolase, hexosekinase, glucose - 6 - phosphate - dehydrogenase (G6PDH), LDH, MDH, ICDH, and others, and have shown that all these enzyme systems are altered during insufficiency. No attempt is made to compare sensitivities. None of these many enzyme systems has been used widely enough to establish reliability and much more work is required to ascertain specificity. GOT particularly, and LDH, on the other hand have had wide study and application and their dependability is established. Also the degree of specificity and sources of error have been thoroughly investigated. It seems unlikely, therefore, that any of the more recently investigated systems will soon replace them in the diagnosis of myocardial infarction. At present isoenzymes carry the most promise for achieving greater specificity and of separating organ systems when the diagnosis is complicated by disease in several organs, for example liver and heart muscle.[16]

Several publications have reiterated that enzyme diagnosis is more sensitive than the electrocardiogram.[3] It has been well established that myocardial necrosis, confirmed by autopsy, can occur without electrocardiographic alteration in the presence of elevated enzyme activity.[17]

The value of enzyme elevation in separating minimal infarction from coronary insufficiency without myocardial necrosis is attested in recent studies.[4,39] Nevertheless, it must be repeated that a diagnosis of myocardial infarction cannot be established by increase in enzyme activity, even in association with pain, electrocardiographic changes, fever and leukocytosis, because such changes are not specific. They can be imitated by pericarditis, myocarditis, dissecting aneurysm, pancreatitis, biliary tract disease and the administration of some drugs.[53] On the other hand when enzyme activity is absent for 48 hours or more after the onset of persistent thoracic pain, then the possibility of infarction is so rare (less than 3 per cent) as eventually to rule out myocardial infarction.

In prognosis, it is still being found that the degree of infarction is roughly correlated with the height of the enzyme rise and thus with the mortality rate,[22,45] but such estimates are only a general guide. In the absence of shock, circulatory failure, or other source of enzyme liberation —from the liver, for example—high enzyme activity does have some relation to an increased mortality.

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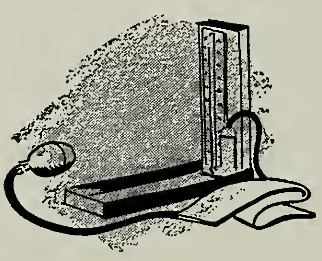

Major Operations on Patients with Poliomyelitic Impairment

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■ *Pertinent data on operations (other than orthopedic) carried out in 39 patients who had residual impairment from poliomyelitis were reviewed with a view to appraising what additional operative risk there may be for such patients.*

For a large proportion of the patients, equipment to aid respiration was needed and a large proportion of the operations were urologic procedures as might be expected in a group with generally restricted physical activity. Also, the occurrence of complications was higher than for an ordinary surgical service. Even so, the experience indicated that residual impairment from poliomyelitis ought not be considered a contraindication even of elective, let alone emergency operations.

WHEN MAJOR SURGICAL OPERATION is proposed for patients with diminished respiratory reserve or decreased locomotor ability residual from poliomyelitis, extra care must be taken in planning the procedure, and equipment must be provided for assisting respiration.

Yet in the recent medical literature there is very little material on this particular subject. In 1945 Metheny and Olson[2] presented the case of a 29-year-old patient confined to a respirator who was operated on for acute appendicitis, with successful outcome. Neu and McCarthy[3] in 1956 reported the case of a 27-year-old man with vital capacity of 1035 ml who underwent left lower lobectomy for bronchiectasis.

Joos, Talner and Wilson[1] in 1956 reported on a series of 17 respirator patients, aged 16 through 35 years, who among them had 21 surgical procedures. Fourteen of the 21 were major operations. The vital capacity of the patients ranged from 5 to 30 per cent of normal. These investigators concluded that "practically any surgical procedure that is clearly indicated can be carried out on these patients without much added risk over that incurred in any patient, but with the need of special care and preparation."

Urologic surgical procedures in postpoliomyelitic patients was the subject of reports by Taylor, Alcock and Hildes[5] on 13 patients, and by O'Connor and Wiener[4] on seven operations on five patients. These observers agreed that the basic cause of the increased calculus formation in patients of this type is prolonged immobility which results in demineralization of bone and hypercalciuria.

Present Study

To add to the rather lean literature on this subject, the medical records of all patients with residual impairment from poliomyelitis who were operated on at Rancho Los Amigos Hospital during the period 1958 through 1963 were reviewed. Orthopedic operations were excluded and the material remaining for study was 62 surgical procedures in 39 patients (Table 1). There were 21 females and 18 males. The age of the patients ranged from 2 to 63 years with an average of 30 years. Twenty-eight of the patients had had bul-

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bospinal poliomyelitis, six were quadriplegic and five were paraplegic.

Equipment to aid respiration was needed for 24 patients. The vital capacity varied from less than 1 per cent of normal to 90 per cent. These 24 patients had 36 complications associated with the surgical procedures.

The length of stay in hospital that was related to the surgical operation ranged from 6 to 190 days and the average was 32 days. There was one postoperative death.

Operative Procedures

Urinary Tract

Seventeen patients, nine male and eight female, had among them 25 operative procedures on the urinary tract (Table 2). The age range was 7 to 43 years and the average 26 years. Fifteen of the patients had had bulbospinal poliomyelitis and two were quadriplegic. For 13 of them respiratory assistance was needed. The vital capacity ranged from 1 per cent to 58 per cent of normal. Nineteen complications of operation occurred in 12 patients (Table 3). The duration of stay in hospital varied from 8 to 190 days, averaging 49. There were no operative deaths in this group.

Gastrointestinal Tract

Fourteen patients had among them 16 operations on the gastrointestinal tract involving the performance of 19 surgical procedures (Table 4). Eight of the patients were female, six male. The age range was 15 to 63 years and the average 38 years. Eight patients had impairment from bulbospinal poliomyelitis, three were paraplegic and three were quadriplegic. Respiratory equipment was needed for ten patients. The vital capacity varied from 1 per cent to 60 per cent of normal. Seven patients had 12 complications related to the operation (Table 5). The duration of hospital stay ranged from 6 to 46 days, the average being 16 days. One patient, a 26-year-old man who had had gastrostomy, died of atelectasis and pneumonia 19 days after operation.

TABLE 1.—*Operative Procedures on Patients with Poliomyelitis, 1958-1963*

Location	*Number*
Urinary tract	25
Gastrointestinal tract	19
Female reproductive tract	6
Intrathoracic	6
Miscellaneous	6
Total	62

TABLE 2.—*Operative Procedures on the Urinary Tract*

Procedure	*Number*
Ureterolithotomy	7
Nephrolithotomy with nephrostomy[4]	5
Pyelolithotomy with nephrostomy[1]	7
Nephrectomy	4
Pyeloplasty	2
Total	25

Intrathoracic Operations

Six patients, three male and three female, had intrathoracic procedures — lobectomy in three

TABLE 3.—*Morbidity Associated with Urinary Tract Operations*

Complication	*Number*
Wound infection	6
Pyelonephritis	4
Recurrent stone formation	2
Pneumonia	2
Ileus	1
Bacteremia	1
Septicemia	1
Grand mal seizure	1
Gastric hemorrhage	1
Total	19

TABLE 4.—*Operative Procedures on the Gastrointestinal Tract*

Procedure	*Number*
Cholecystectomy	6
Gastrostomy	6
Appendectomy	4
Subtotal gastrectomy	1
Choledochostomy	1
Repair esophageal hiatal hernia	1
Total	19

TABLE 5.—*Morbidity Associated with Gastrointestinal Tract Operations*

Complication	*Number*
Atelectasis	4
Pneumonia	3
Ileus	1
Hypotension	1
Subphrenitis	1
Wound infection	1
Thrombophlebitis	1
Total	12

TABLE 6.—*Miscellaneous Operative Procedures*

Procedure	*Number*
Abdominal exploration	2
Lumbar sympathectomy	2
Orchiectomy	1
Hemithyroidectomy	1
Total	6

cases, thoracotomy for cardiac arrest in three. Four of the patients had residual effect from bulbospinal poliomyelitis, one was quadriplegic and one was paraplegic. For two of them respiratory equipment was needed. The vital capacity varied from 3 per cent to 90 per cent of normal. Two patients had postoperative complications, pneumonia in one case, acute gastritis in the other. Stay in hospital ranged from 12 to 60 days and the average was 36. There were no operative deaths in this group.

Female Reproductive Tract

Four women had four operations on the reproductive tract, in which six surgical procedures were done, abdominal hysterectomy in three cases and salpingo-oophorectomy in three. The age of the patients ranged from 29 to 48 years, the average being 37. Three of the patients had impairment from bulbospinal poliomyelitis and one of them was quadriplegic. Equipment to aid in respiration was needed for two patients. The vital capacity varied from 10 to 60 per cent of normal. Postoperative complications occurred in two cases, ileus in one, atelectasis in the other. Stay in hospital ranged from 16 to 19 days and the average was 13 days. There were no operative deaths.

Miscellaneous Operations

Six patients, four female and two male, had operations not included in the classifications already discussed (Table 6). The age range was 10 to 54 years (average 31 years). Three patients had residual damage from bulbospinal poliomyelitis and three were paraplegic. For three of them respiratory equipment was needed. The vital capacity varied from 8 to 90 per cent of normal. One patient had a postoperative complication—pneumonia. The shortest stay in hospital was six days, the longest 13 days and the average nine days. There were no postoperative deaths.

Discussion

As the average age of the patients in this series was only 30 years and the oldest was only 63, the chronic medical diseases of the aged, which are known to play a prominent role in the morbidity and mortality associated with major surgical procedures, were not a considerable factor.

The variety of surgical procedures performed was in keeping with what might be expected in a predominantly young group. The preponderance of urologic procedures reflects the known difficulty of avoiding calculus disease of the urinary tract in bedridden patients. In a series of this kind, gastrostomy in six of 39 patients cannot be considered inordinately high, since the procedure is one that is helpful in the rehabilitation of patients who have difficulty in swallowing as a residual impairment of poliomyelitis.[6]

One of the most obvious features in this series was respiratory deficiency. For 24 of the 39 patients, mechanical respiratory equipment was needed to maintain adequate ventilation. The average vital capacity of all patients was 26 per cent of normal. Taking this fact and the generally good results together, diminished respiratory reserve ought not be considered a contraindication even to elective, let alone emergency operation. As long as adequate facilities and nursing care are available, the great majority of patients can be carried through postoperative convalescence quite safely. The one death in the series was caused by pneumonia and atelectasis, but as with any death in a situation of greater than normal risk, the possible hazards must be weighed against the necessity for operation.

The incidence of complications was higher than would be expected for an average surgical service. The highest incidence was associated with operations on the gastrointestinal and urinary tracts and the complications were mainly respiratory or urologic in nature. Atelectasis and pneumonia frequently delayed the recovery of patients who had decidedly diminished vital capacity. Among patients with calculus disease of the upper respiratory tract, pyelonephritis was a frequent complication. The difficulty in treating renal calculus disease in patients of this category is reflected in the multiplicity of surgical procedures—25 operations for 17 patients.

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Ocular Complications of Chloroquine Therapy

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■ *Long-term therapy with chloroquine can lead to irreversible retinal damage and serious loss of visual acuity and visual field. Not only are the retinal changes irreversible but they may continue to progress after discontinuance of the drug. Work is proceeding on the development of electrophysiological techniques for early detection of toxic effect before significant retinal damage occurs. Another possibility for minimizing the toxic effect of chloroquine is the use of other drugs which increase the excretion of chloroquine from the body.*

CHLOROQUINE is one of the group of synthetic antimalarial agents which are now widely used in the treatment of lupus erythematosus, chronic arthritis, sarcoid, asthma, collagen diseases, amebiasis and actinic dermatitis. All the commonly used synthetic antimalarial agents have been incriminated in toxic ocular effects of one kind or another. The list of such drugs includes chloroquine phosphate (Aralen®), chloroquine diphosphate (Resochin®), hydroxychloroquine (Plaquenil®), amodiaquin (Camoquin®), quinacrine hydrochloride or mepacrine (Atabrine®), quinine-hydroxyquinone, and a combination of chloroquine phosphate, hydroxychloroquine, and Atabrine, known as Triquin.® Of these, Atabrine is not used much now because it colors the skin and has been known to cause aplastic anemia.

Since 1955 reports have been accumulating of the ocular toxic effect of these drugs.[8,9,14] Chloroquine was used originally in the treatment of malaria, but eye toxicity was not a common concomitant of this use, for the doses were smaller and the period of treatment shorter.

While it must be noted that some of the diseases treated with chloroquine may themselves cause eye changes, these changes are not those associated with chloroquine toxicity. For example, in systemic lupus erythematosus there may be primary involvement of the vascular system of the retina with cotton-wool exudates, hemorrhages and capillary aneurysms in the fundus, but these are distinct from the changes noted with chloroquine.

Effects

The first reports of chloroquine toxicity made note of various ocular signs and symptoms which, fortunately, were reversible with discontinuance of the drug. Deposits in the corneal epithelium[4] were noted. Occasionally, according to the early reports, there was some corneal edema and the patient would report haloes around lights. There were a few reports of poliosis, paralysis of accommodation and extra-ocular muscle palsy with diplopia, but the most consistent finding was that

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of epithelial or subepithelial corneal deposits and striations. Roughly 40 per cent of patients who were examined carefully had such changes in the cornea which usually did not appear before several months of fairly high doses of chloroquine. These changes would disappear two or three months after discontinuance of the drug.

More recently, reports have been accumulating of irreversible changes in the retina with serious loss of visual acuity and visual field.[5-7,10-13,16] This has been reported to occur in about 15 per cent of patients taking large doses of chloroquine, and it usually takes at least a year or two for the retinal changes to appear. In most cases the patients had been taking anywhere from 200 to 1,000 mg daily for 2 to 4 years when the retinal changes were first noted. Not only are the changes irreversible, but they may continue to progress after cessation of chloroquine therapy.

Report of a Case

A woman 62 years of age reported for ocular examination because of decreasing vision for eight months. For ten years she had been taking 500 mg of chloroquine daily for chronic rheumatoid arthritis. With best correction she had distance visual acuity of 20/60 in each eye—not good enough to pass a driving test. Her reading visual acuity was reduced to Jaeger No. 10 print—not sufficient for comfortable reading of a newspaper. On ophthalmoscopic examination, large, round pigmented lesions were seen in the maculae of both eyes (Figure 1). Visual field testing showed large central scotomas in each eye.

Pathologic Changes

The retinopathic change in such cases consists of a pigmentary degeneration of both the central and peripheral retina. The macula is often involved first and visual acuity may diminish to such a degree that the patient may be able to see only well enough to count fingers. Along with the pigmentary changes there is sometimes narrowing of the arterioles and pallor of the optic nerve. Usually the defects in the visual fields are central or paracentral but sometimes there may be peripheral constriction, altitudinal defects, quadrantic defects or hemianopsia. The changes are always bilateral. Besides loss of visual acuity, the patient may lose ability to distinguish colors. Perception of blue usually is the first to go, the patient often stating that things look reddish. The macular changes usually occur first and the peripheral pigmentary changes come about late in the disease. Adaptation to dark is affected late. In advanced cases the electroretinogram shows a decreased response.[6,13,18]

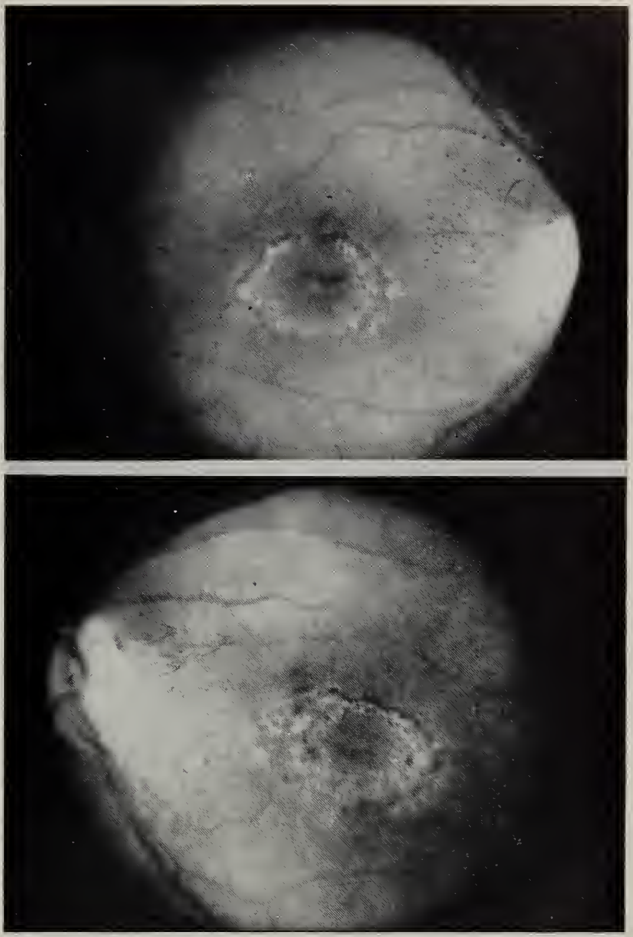

Figure 1.—Macular degeneration of the eye (the lower picture is of the left eye) secondary to chloroquine toxicity.

A new technique of using electro-oculography as an electroretinographic test shows promise; if it leads to early detection of chloroquine toxicity, the retinopathic changes probably can be avoided.

The ophthalmoscopic appearance of changes caused by chloroquine toxicity is a little like that of retinitis pigmentosa, but distinguishing between the two is not difficult.[13] The visual field scotomas in chloroquine toxicity are more central than the ring scotomas of retinitis pigmentosa. Dark adaptation is affected later in the course of chloroquine toxicity than in retinitis pigmentosa. The electroretinogram in chloroquine toxicity shows a greater cone loss than rod loss; in retinitis pigmentosa it is the other way around. The peripheral pigmentary changes occur late in chloroquine toxicity, early in retinitis pigmentosa. Histologically, the pigment accumulations in chloroquine toxicity are in the outer retinal layers, whereas in retinitis pigmentosa they are seen around blood vessels and in the inner layers of the retina.

Reports of tissue examination were included in two recent cases. In one of them[17] a patient who had been taking chloroquine for about seven years died. Clinically a paracentral scotoma breaking through to the superior periphery had been noted. The electroretinographic response was decreased. On gross inspection of the eyes at autopsy, only darkened foveas were noted. Under the dissecting microscope, small, white, opaque dots which fluoresced under ultraviolet light were seen in the retina. (Fluorescence is said to indicate deposits of chloroquine.) Microscopic examination indicated severe and widespread reduction in the rods and cones and their nuclei. The fovea and a few temporal areas of retina were spared. There were pigment accumulations in the rod and cone layers. Similar histological changes were reported in the second case.[3]

Pathogenesis

The mechanism by which chloroquine causes this damage to the retina is unknown. It would appear to be more than an individual idiosyncrasy, although two different effects were noted in patients who were identical twins.

There has been much theorizing and speculation as to the pathogenesis of the visual degeneration. It appears that in some way the metabolism of melanin is involved. Animal experiments with rabbits and cats have shown a remarkable predilection of chloroquine for pigmented uveal tissues—that is, the choroid and the iris.[2] Chloroquine persisted in high concentration in the uvea of these animals for long periods. Melanin pigment may play a principal role therefore in binding the drug. The abnormalities in the electrodiagnostic tests suggest defects in the retinal pigment epithelium, again incriminating melanin. It is thought that perhaps the defects in the pigment epithelium lead to degeneration of the retinal photoreceptors, the rods and cones.

Another theory postulates that chloroquine poisons important enzymes in the visual purple cycle or enzymes necessary for macular function. There is also some evidence that chloroquine reacts strongly with nucleic acids and nucleoproteins. This may explain why chloroquine becomes localized in tissues but does not explain why it has such an affinity for the rods and cones.

One of the major questions in this field is: Why do the retinopathic changes progress after cessation of drug therapy? The answer is probably related to the prolonged retention of chloroquine in ocular tissues. Chloroquine is selectively distributed throughout various tissues of the body and excreted very slowly. In one report, chloroquine was found in the plasma, in red blood cells and the urine of a patient with chloroquine retinopathic changes as long as five years after the last known ingestion of the drug.[15]

Discussion

In view of the hazards, it is wise to restrict the use of chloroquine to diseases for which there is no other available therapy or the danger of the disease outweighs the danger of blindness. It is a good idea to have an eye examination before starting long-term therapy, including fundus photographs if possible. It is further suggested that an eye examination be performed about every three months, including slit lamp, ophthalmoscopic, color vision and visual field examination, electroretinograms and determination of adaptation to dark. The drug should be discontinued at the first sign of visual field reduction, loss of visual acuity or color vision or ophthalmoscopic change. It might be worthwhile to interrupt the administration of the drug from time to time.

Because progression of the retinopathic changes after discontinuance of the drug might be related to prolonged retention and high tissue levels, methods of increasing chloroquine excretion have been sought.[15] It has been found that acidification of the urine by oral administration of ammonium chloride can cause a 20 to 80 per cent increase in urinary excretion of chloroquine in patients taking the drug daily. It has been suggested that a therapeutic regimen in a case of chloroquine toxicity would be ammonium chloride, 8 grams per day for three days, repeated each week for a minimum of six to eight weeks. It has also been found that dimercaprol (BAL) caused doubling or trebling of chloroquine excretion. The necessity for intramuscular injection and the unpleasant (but not serious) side effects, limit the use of BAL to relatively short terms. The recommended dosage is 2.5 to 3 mg per kilogram of body weight administered intramuscularly four to six times daily for the first three days, then every 12 hours for ten days. There is no evidence yet that the use of these measures to increase chloroquine excretion will reverse the retinopathic changes or prevent further damage.

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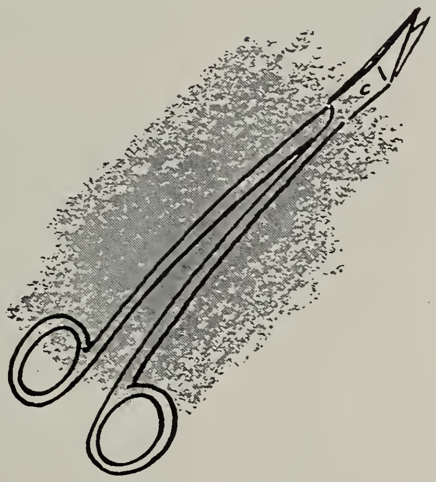

REVIEW ARTICLE

Induction of Ovulation

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■ *Every effort should be made to find the cause of anovulation since specific therapy directed at correction of a specific hormonal deficiency or excess is, of course, much more effective than any empiric treatment. Moreover, some patients with disorders of ovulation may have serious, even fatal, underlying disorders. The use of thyroid or cortisone has been disappointing except in the treatment of an overt deficiency of thyroid or cortisone or an excess of adrenal androgens. Estrogens and progestational agents have not been consistently effective in the induction of ovulation. The use of clomiphene citrate, which apparently stimulates the release of gonadotropins, and the use of purified gonadotropins of human origin have been quite successful in the induction of ovulation in a variety of disorders of ovarian function. Because of real and potential hazards, the use of these new agents should be restricted to women for whom pregnancy is the primary goal or in whom standard methods of therapy have failed. Neither drug has been released by the Food and Drug Administration for routine clinical use.*

SEVERAL EFFECTIVE METHODS for the hormonal induction of ovulation in humans have been developed in the last few years. The preparation of highly purified extracts of human gonadotropins and the synthesis of pharmacologic agents which activate the release of endogenous gonadotropins are significant advances in gynecological endocrinology for which there is immediate clinical application. Use of these newer agents in the treatment of amenorrhea and other disorders of ovulation promises a much greater success rate than was thought possible a few years ago. This review will discuss these newer agents in addition to the other hormonal agents, such as desiccated thyroid, cortisone and estrogen, that are currently used for the stimulation of ovulation.

Since different mechanisms of the control of ovulation make interpretation difficult, studies in lower animals will not be discussed unless the results seem directly applicable to humans and data from comparable studies in the human are not available. Treatment of anovulation by surgical operation, by radiation or by therapy of specific diseases associated with ovulatory failure will not be discussed except in passing. In many cases a review article or a single recent report will be cited when actually many are pertinent. The interested reader may thus be one step away from the source material. The search of the literature for this review, completed in December 1964, concentrated upon reports appearing subsequent to the publication of a series of excellent critical review articles by Kotz and Herrmann which appeared in the 1961 volume of the journal *Fertility and Sterility*.[46-51]

Indications for the Induction of Ovulation

In the patient who ovulates infrequently or not at all every attempt should be made to determine a cause and to correct any specific disorder. In many patients, however, no correctable disorder

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will be found. If these patients wish to ovulate in order to become pregnant, the indication for induction of ovulation is clear and in most cases strong enough to warrant the use of methods available today. Patients with anovulation manifested by excessive or irregular uterine bleeding, amenorrhea or oligomenorrhea can now be made ovulatory and potentially fertile. This includes patients with psychogenic amenorrhea, hypothalamico-pituitary dysfunction and patients with the Stein-Leventhal syndrome of polycystic ovaries, infertility and menstrual abnormalities. Although, at present, most of these conditions are managed by therapy with estrogens or progestogens, in the future they may best be managed by repeated cyclic stimulation of ovulation even if pregnancy is not the primary goal. Since the drugs now being tested for induction of ovulation carry with them known hazards and risks as well as the unknown hazards of any new drug, use of them in unmarried patients or those not concerned with fertility is not yet warranted unless standard methods of treatment have failed. The use of ovulatory stimulants for the prophylaxis of hyperplasia or carcinoma of the endometrium or fibrocystic disease of the breast in anovulatory patients must be judged by the same standards as are now used in the evaluation of substitutional progestational therapy for prevention of these conditions.

The indications for induction of ovulation in patients who ovulate regularly are much less clear and not sufficiently strong to warrant the use of currently available methods. There is little basis for the use of ovulatory stimulants in cases of unexplained infertility except to determine beforehand the date of ovulation so insemination by the usual or by artificial means may be carried out at the appropriate time. Although the incidence of anovulatory cycles is higher in infertile patients than in the general population, this is probably accounted for by patients with irregular cycles. Since anovulation occurs in only about 5 per cent of cycles in regularly bleeding women,[46] the risks and uncertainties of present methods of ovulation induction are unwarranted in infertile patients with regular cycles and other indications of regular ovulation. Even infertile patients whose menstrual pattern is somewhat irregular or whose cycle is somewhat longer than usual probably should not now be considered for induction of ovulation if the majority of cycles are ovulatory.

TABLE 1.—*Methods for the Detection of Ovulation*

History of regular cycles
Basal body temperature
Cervical mucus changes
Vaginal cytology
Endometrial biopsy
Urinary chemical assays
Physiochemical changes
Direct observation of corpus luteum
Pregnancy

Diagnosis of Anovulation

Since attempts at induction of ovulation should be limited to those patients with evidence of consistent absence of ovulation, brief mention will be made of methods of detection of ovulation. All infertile patients and patients with irregular menstrual cycles should be investigated for the presence of ovulation. The methods in Table 1 have been the subject of several recent critical reviews.[2,12,32,46] They are listed in the order of their clinical utility. The clinically practical methods are indirect, individually less reliable and, therefore, best used in parallel and serially.

Increased secretion of progesterone, which is produced in relatively small amounts before ovulation and corpus luteum formation, provides the basis for most of the clinically applicable methods of ovulation detection. It follows that none are useful in the prediction of ovulation. A consistent biphasic pattern of basal body temperature, with an increase of approximately 0.5 degrees Fahrenheit following ovulation caused by the thermogenic action of progesterone and its metabolites, is an excellent index of ovulation against which most other methods are judged. It should

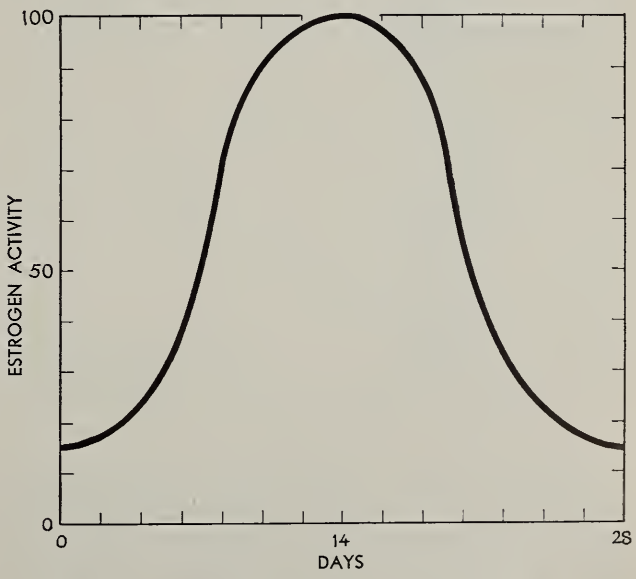

Chart 1.—Typical "haystack" pattern of measurement of estrogen activity (on a scale of 100) during menstrual cycle. The decline from ovulation on the fourteenth day is owing to antiestrogenic activity of progesterone, which decreases the biologic effects of estrogen.

be noted that the basal temperature does not indicate with any degree of accuracy the exact day of ovulation.

Increasing levels of estrogen before ovulation followed by increasing levels of progesterone after ovulation result in a "haystack pattern" when any one of a number of factors easily measured clinically is plotted against time (Chart 1). This occurs because the antiestrogenic activity of progesterone effectively decreases the biologic effects of estrogen. Increasing estrogen activity results in progressive increase in the amount of cervical mucus, its clarity, stretchability (*spinnbarkeit*) and degree of crystallization after drying (*mucus fern*). After ovulation these effects are reversed by the secretion of progesterone. The content in the mucus of glucose and of salt plays a role in the production of these characteristics and can be measured directly with simple test papers.

A similar haystack pattern is seen if the per cent of mature cornified cells (cornification index, CI) or cells with pyknotic nuclei (karyopyknotic, index KI) in smears of exfoliated vaginal cells is plotted against time.

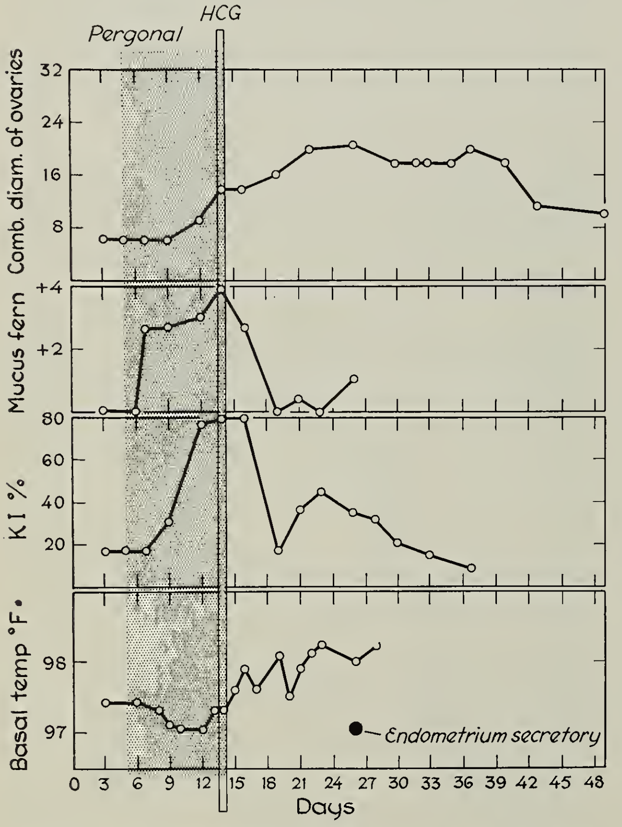

Chart 2.—Changes in clinically detectable factors in a patient treated with exogenous gonadotropins. *KI*=karyopknotic index, the per cent of desquamated vaginal cells with small dense nuclei. *Mucus fern*=degree (one plus to four plus) of fern-like crystallization of the mucus after drying. The large black dot indicates the time of endometrial biopsy. *Comb. diameter of ovaries* refers to the sum of the estimated diameters in centimeters of both ovaries; for example, bilateral 8 cm cysts=16.

Note the persistence of ovarian enlargement during early pregnancy.

Biopsy of endometrial tissue taken late in the cycle or at the onset of menstruation will demonstrate the characteristic secretory effects of progesterone on the endometrium. The use of these clinically applicable factors in the study of an induced ovulatory cycle as shown in Chart 2.

Methods that require operative intervention for observation of a corpus luteum or recovery of an egg, and methods requiring serial determinations of pregnanediol or other steroid metabolites, although of high reliability, are obviously impractical for even one cycle. Patients studied by these methods and those who have become pregnant after isolated insemination have served to evaluate the precision of the clinically applicable methods. A variety of chemical assays of urinary metabolites and physiochemical techniques including measurement of vaginoabdominal potential differences, vulvar fluorescence, kymographic oscillations of the fallopian tubes, action potentials of the uterus, etc., have been described but have not found clinical acceptance.

Review of the standard textbooks of gynecology or endocrinology will reveal a large number of diseases which may be associated with ovulatory failure. In many, such as hypothyroidism, Cushing's syndrome, psychosis and malnutrition, ovulatory failure is a minor part of the problem and its correction will accompany successful therapy of the primary disorder. The patient will profit little from advances in endocrine therapy unless systematic efforts have been made on her behalf to be certain that there is no illness threatening her life or health. Once this has been established, nonspecific and empirical therapy may be indicated for those in whom no correctable disorder has been found. Although treatment with gonadotropins or with recently developed steroidal and non-steroidal agents may well be specific therapy for certain hypothalamic and pituitary disorders, this report will deal mainly with non-specific and empirical methods of ovulation induction.

Indirect Methods of Ovulation Induction

The following logic is the basis for a number of treatment programs designed to stimulate ovulation in anovulatory patients: severe deficiencies of certain hormones (for example, in Addison's disease and myxedema) are associated with anovulation and amenorrhea, and replacement therapy results in resumption of ovulation; perhaps many unexplained cases of anovulation are due to subclinical deficiencies which would respond equally well to treatment with hormones, perhaps even in low doses proportionate to the severity of the deficiency.[46] Happily many cases of idiopathic anovulation are self-limited and respond to observation, placebo therapy or any one of a variety of non-specific remedies.[106] Without double-blind tests, however, interpretation of the results of therapy with these non-specific remedies is overwhelmingly difficult and, unfortunately, few such studies have been carried out. In many instances the regimens described in the literature have been proposed by enthusiasts who would feel it unfair to deprive their patients of the chance to share in the uniformly excellent results.

The proposed physiologic basis for these methods, of course, varies somewhat with the particular hormone prescribed, but in most instances is based on one of the two following premises: (1) The hormone prescribed sensitizes the ovary to respond more easily to ambient concentrations of gonadotropins, (2) the medication somehow causes the release of gonadotropins from the pituitary to cause ovulation. In some cases these effects are brought about by suppression of another hormone or factor which inhibited ovulation. In most instances there is evidence from animal experimentation to support either thesis, but, also, it must be stated that there is often equally convincing animal data to support the opposite conclusion—that is, that such treatment will inhibit ovulation. The hazard to the patient in the use of these empirical regimens is twofold: (1) adequate diagnostic studies may be omitted in the haste to provide "effective" treatment, (2) if doses beyond the physiologic range are given, the patient may then suffer from the effects of an excess of the hormone which may well include anovulation.

Thyroid

Use of thyroid extract and various synthetic or semi-synthetic analogues of thyroxin, probably the most widespread of empiric therapies for anovulation, is based on the well documented response of patients with anovulation associated with myxedema or hypothyroidism to replacement therapy with thyroid.[47,90] The drug, moreover, is a standard remedy, cheap, readily available and conveniently administered orally. A further advantage is that in reasonably physiologic dose ranges a patient with normal thyroid function will compensate for exogenous thyroid by decreasing the output of pituitary thyrotropin and thus of thyroxin from the thyroid.[28] The result is a convenient escape from many problems of overdosage. The greatest disadvantage of the empirical use of thyroid for the treatment of anovulation is that it has never been shown to be effective in euthyroid patients.[47] Suppression of thyrotropin which provides the safeguard also implies that the administration of thyroid to normal patients for the control of anovulation (or obesity or fatigue) is virtually without promise of therapeutic effect since excessive amounts would be required before elevation of the levels of circulating thyroxin or effects on metabolism would be produced.[28] Although there have been innumerable clinical reports of the use of thyroid in a variety of conditions related to ovulation, there have been few controlled studies of the use of thyroid extract in the treatment of anovulation. Even in the less well controlled studies in which the results in groups with and without treatment were compared, no effect of thyroid therapy could be demonstrated in euthyroid subjects. In cases in which there is some evidence of possible decreased thyroid function such as a low or borderline protein-bound iodine (PBI), the results are, of course, somewhat better but conclusive only in cases of true hypothyroidism.

The presence of thyroid hormone is, of course, necessary for the proper function of innumerable cellular processes, undoubtedly including those related to gonadotropin and steroid production, development of the follicle and ovulation. The effects of thyroxin on the production and release of pituitary gonadotropins and their action on the ovary has not been extensively studied. Such evidence as is available would suggest an increase in ovarian activity with low circulating thyroxin associated either with an increased secretion of gonadotropin as well as thyroid stimulating hormone (TSH) or with a diminished deactivation of gonadotropin.[61] In humans the coexistence of myxedema and precocious puberty with elevated excretion of gonadotropins has been described.[38] Production of a polycystic ovary syndrome with disorders of the estrus cycle in rats by injection of chorionic gonadotropin is possible only in animals treated with antithyroid drugs or that have had the thyroid gland removed.[33,101] Development of the syndrome is prevented by the administration of thyroxin but, once the syndrome is established, thyroxin therapy is without effect. In several laboratory animals the administration of thyroxin will decrease the sensitivity of the ovary to exogenous gonadotropins but there is a definite variation between species.[61,68] Moreover, at low doses there seems to be some increase in ovarian response in those animals in which the response is inhibited at higher doses. Thyroxin is known to have an effect on gonadal enzyme systems which play a part in the intermediary metabolism of various androgenic and estrogenic steroids.[20] What effects these changes might have on the induction of ovulation are not clear.

Cortisone and Its Analogues

The syndrome of congenital adrenal hyperplasia caused by a deficiency of one of several enzymes necessary for the conversion of steroid precursors to cortisol is characterized by virilization and, in some varieties of syndromes, by salt loss or hypertension. A diagnostic pattern of steroid metabolites is evident in the urine at birth.[5] The syndrome of the most common type, if untreated, will result in amenorrhea in adult females. When treated with cortisone, such patients have ovulatory cycles and are fertile.

There are women who manifest one or more of the signs and symptoms of adrenal overactivity such as hirsutism, menstrual disorder, change in libido, obesity and/or elevated urinary 17-ketosteroids with normal or even relatively low excretion of 17-hydroxysteroids or 17-ketogenic steroids.* Many terms have been applied to this group of disorders but the most common is "mild adrenal hyperplasia" despite the fact that the specific enzymatic deficiencies found in congenital adrenal hyperplasia have rarely been noted in patients with virilization of adult onset except in cases of adrenal tumor.[56] Many patients with these symptoms will have disorders of ovulation, smooth, often enlarged, ovaries and will be classified as having the Stein-Leventhal syndrome.[9,27,55,60] The assumption is made that an enzymatic defect exists and that suppression of ACTH and replacement of the necessary amounts of cortisol will result in "normalization" of the altered adrenal steroid secretion and a decrease in secretion of adrenal androgens that have directly or indirectly prevented ovulation.[27,50,55,60] The finding that treatment with cortisone results in a decreased urinary excretion of 17-ketosteroids in this group of patients does not support the assumption of an enzymatic deficiency, since a similar decrease is seen in normal patients. Large numbers of patients with "mild adrenal hyperplasia" have been studied in an attempt to find a unifying theory to explain the findings. Some of them have a greater than normal sensitivity to ACTH, others have increased concentrations of potent androgens in blood and urine. Despite lack of knowledge of the exact mechanisms at work in this heterogenous group, it has been found that treatment of these patients with cortisone or its analogues will sometimes result in ovulation and fertility. If specific disorders of the gonads or the adrenal glands can be excluded by appropriate studies, a trial of cortisone therapy in the physiologic dose range equivalent to 15 to 50 mg of cortisone acetate per day is thought warranted.

The use of cortisone has been extended by some clinicians to patients with no evidence of adrenal disorder and normal urinary levels of ketosteroids.[36,39,50] Excellent results are reported but the studies are entirely uncontrolled.

The mechanism of action of corticosteroid therapy is well defined in the congenital adrenal hyperplasia syndrome: suppression of ACTH resulting in suppression of adrenal cortical production of both cortisol, and the androgenic adrenal steroids which have caused the clinical manifestations. The effectiveness of cortisone in the cases classified as "mild adrenal hyperplasia" is more difficult to explain since the physiologic basis is less well understood. The goal is the same—to reproduce the normal pattern of adrenal steroid concentrations in the blood.

To justify the use of corticosteroid therapy in patients with normal adrenal function, one must seek another mechanism of action based on the effects of excess cortisone on gonadotropic or ovarian function. Increased circulating levels of cortisone and decreased levels of the other adrenal cortical hormones and of ACTH may have effects on the gonadotropin controlling centers or directly on the ovary and its steroid synthetic mechanisms. In man, administration of cortisone results in increased urinary excretion of gonadotropins and estrogens[9] and alteration of the intermediary metabolism of estrogens and androgens.[1,107]

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*Reference Nos. 5, 6, 34, 36, 42, 50, 69, 91.

Estrogens and Related Compounds

Despite several encouraging reports, the use of estrogenic compounds to induce ovulation has not been popularly accepted.[48] They are, however, frequently used in the treatment of patients with anovulation since, administered cyclically in sufficient doses, they result in regular uterine bleeding accepted by the patient as a sign of normal reproductive tract function. The goal is not to stimulate ovulation but to simulate the cyclicity absent in anovulatory patients.

Oral or intravenous administration of single or intermittent high doses of estrogens has been stated to result in ovulation in a significant percentage of anovulatory patients.[52] The use of intravenous estrogen in high doses has been proposed as a test for the sclerocystic ovary syndrome since those patients who do not respond are considered to show ovulatory blockade at the ovarian level. Kupperman, the most widely quoted advocate of intravenous estrogen therapy for anovulation, reports successful induction of ovulation in over 50 per cent of selected patients. Other investigators, however, have had difficulty in duplicating these results.[48]

High dose estrogen therapy is based on the action of estrogen on the hypothalamico-pituitary control of gonadotropin secretion. A rapidly increasing concentration of estrogen—for example, that produced by the developing follicles during the normal cycle— upon reaching the hypothalamus is thought to promote the release of luteinizing hormone (LH) and suppress the release of follicle stimulating hormone. (FSH) by the pituitary. Studies of urinary excretion of estrogens and total gonadotropins in normal cyclic women show variation in which of the two reaches its peak of excretion first in the cycle.[7,43,57,99] Assays specific for LH and FSH have not yet been carried out following short term, high dose estrogen therapy in humans.

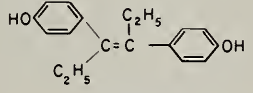
Administration of continuous low doses of estrogen has been advocated as therapy for anovulation, and excellent results have been reported in uncontrolled studies.[42,48] It has not been demonstrated, however, that such therapy is more successful than any other non-specific remedy.[25]

Estrogen therapy in continuous low doses is designed to increase the sensitivity of the ovary to gonadotropins, a response well documented in laboratory animals.[24,78,94] This sensitization may be a direct effect on the ovary or may be mediated through release of endogenous gonadotropins.[21,86,94] An analogy may also be drawn between the use of low doses of estrogen in some instances of ovarian dysfunction and low dose cortisone therapy in adrenal hyperplasia, since defects in the ovarian metabolic pathways leading to estrogen formation have been described in some anovulatory patients, especially those with hirsutism.[6,27,60]

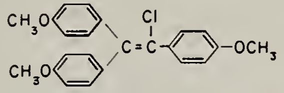
LaBerge and Rock in 1962[53] reported their experience in the use of a stilbestrol derivative with low peripheral estrogenic activity which was thought to facilitate the release of LH. After it was administered, ovulation occurred in about one-third of more than fifty patients with ovulatory disturbances.

Clomiphene

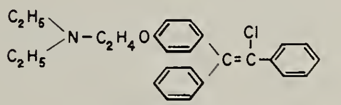
Clomiphene (Clomid, MRL-41, MER-41 or chloramiphene) is an orally administered, non-steroidal agent synthesized by Merrell Laboratories, Cincinnati. Reports of clinical trials with the drug having first appeared about three and one half years ago, it is still under clinical investigation but will probably be considered for release by the Food and Drug Administration in the not too distant future. The structural formula is represented as follows:



STILBESTROL



CHLOROTRIANISENE (TACE)



CLOMIPHENE

From its action in rats, clomiphene was expected to exhibit pituitary-suppressive and antifertility effects in the human. In early clinical studies it became apparent that ovulation was stimulated, not suppressed. Subsequently, induction of ovulation in women with a wide variety of disorders associated with ovulatory failure was reported.

Although non-steroidal, clomiphene has many pharmacological actions similar to those of steroidal compounds, a similarity it shares with its chemical relatives stilbestrol and chlorotrianisene (TACE). As judged by its effects on the size of the rat uterus, clomiphene has both an estrogenic and an antiestrogenic activity.[88] Given alone, it causes an increase in uterine weight but, given along with an estrogen, such as estradiol, it inhibits the uterotrophic activity of the estrogen. This antiestrogenic activity of clomiphene is shared with other estrogens such as estrone, some progestational agents, androgens and other steroidal and non-steroidal compounds.[103a] In human females this antiestrogenic activity is manifested by regression of the estrogenic effects on the vaginal cells and cervical mucus and by the failure of exogenous estrogen to cause suppression of ovulation when clomiphene is given concurrently.[80,87]

The exact mechanism of action of the drug is a matter currently under intensive clinical and laboratory investigation. One hypothesis is that clomiphene competes with natural estrogen for the binding sites in the uterus, pituitary and hypothalamus and effectively displaces it. This mitigates the inhibitory influence of estrogen on the hypothalamico-pituitary axis and causes release of pituitary gonadotropins resulting in ovulation.[87,88]

There is considerable evidence that clomiphene does effect its ovulatory action primarily through stimulation of the pituitary gland or its hypothalamic regulators. Although it should be noted that a few investigators[11,96] have found no change in the excretion of urinary gonadotropins following clomiphene administration, most studies have demonstrated an elevation of total urinary gonadotropin excretion.[33a,73,87]

The change in gonadotropin excretion may occur several days or weeks after clomiphene administration. This has been interpreted as evidence of an indirect action through alteration of the steroid secretion pattern of the ovary. Ovarian enlargement and cyst formation, noted especially with higher doses, bear a striking resemblance to the effects seen after the administration of human gonadotropins both in gross appearance and in the effects on in-vitro steroid synthetic activity.[87,96] An increased incidence of multiple pregnancies is also common to clomiphene and gonadotropin therapy.[26,87] Patients with panhypopituitarism or with hypogonadotropic hypogonadism show diminished or absence of response to clomiphene therapy.[40,80,96] Some women experience hot flashes while taking clomiphene, especially with the larger doses.

Urinary estrogen excretion is increased in both male and female patients following clomiphene therapy.* In the few studies in which simultaneous measurements of estrogens and gonadotropins have been done no consistent relation between the patterns of excretion of the two hormones has been noted.[11,40,73,104] The same lack of correlation exists, however, in women with normal menstrual cycles.[7,43,57]

A number of findings suggest that clomiphene may cause a relative increase in the proportion of luteinizing hormone activity in addition to an increase in total gonadotropins. Increased excretion of 17-ketosteroids occurs in males but not in females, a response seen also after administration of human chorionic gonadotropins.[35,71,72,87,92] Clomiphene has been successfully used in place of human chorionic gonadotrophin (HCG) to "trigger" ovulation in amenorrheic patients stimulated with human postmenopausal gonadotropin (Pergonal).[103] There is some evidence that patients with estrogenic stimulation of the vaginal cells and endometrium, indicating follicular activity, more often respond to clomiphene therapy than those lacking follicular activity.[40] Administration of clomiphene following the rise in basal body temperature will prolong the duration of the "post-ovulatory" phase,[87] an action that can be brought about also with HCG and progestational agents. Clomiphene is not progestational in itself. Finally, studies in which urinary gonadotropin assays specific for FSH and LH have been done demonstrate a significant increase of LH activity in urine following clomiphene administration.[87]

There is also evidence for a direct action on the gonadal enzyme systems responsible for steroid synthesis in addition to its action on the pituitary-hypothalamic system. In addition to an increase in total estrogen excretion, there is an alteration in the relative proportion of the various estrogenic steroids excreted by patients following clomiphene therapy[11,96] indicating an effect on the intermediary metabolism of estrogens. Studies on placental extracts *in vitro* also suggest such an effect.[95]

Induction of ovulation in about 70 per cent of those anovulatory women treated has been reported (see Table 2). Best results, as would be expected, have been in patients with normal results in tests of hormonal excretion who are classified as having "idiopathic," "psychogenic" or "hypothalamic" anovulation. Patients diagnosed

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*Reference Nos. 11, 72, 73, 80, 96, 104.

TABLE 2.—*Results of Clomiphene Treatment of Anovulation as Reported by Various Investigators*

Author	*Number of Patients*	*Number Ovulating*	*Number Pregnancies*[*]
Roy[87]	179	139	31
Payne [76]	63	38[†]	14
Whitelaw[108]	52	41	17
Riley[80]	34	16	5
Naville[73]	36	28	8
Vorys[104]	32	26	9
Total	396	288 (73%)	84

[*] Note that the actual "pregnancy rate" is higher than could be calculated from this table since some of the patients were not desirous of pregnancy.

[†] "Improved ovarian function."

as having Stein-Leventhal syndrome have also responded in a high proportion of the cases reported. Clomiphene appears to be effective therapy for some patients with persistent lactation and amenorrhea.[40,76,87] Although success has been reported in the treatment of a few patients with elevated urinary gonadotropins,[73,76] the majority, including menopausal and climacteric patients, have not responded.[11,73,104] The dose range used in most recent studies has been 25 to 200 mg a day for one to five days. With this dosage the incidence of ovulation has been equal to that found with larger doses over longer periods of time and the side effects of ovarian cyst formation and hot flashes have been less prominent. These side effects regress spontaneously with cessation of therapy. Because of the structural similarity to MER-29 (Triparanol) which also contains the p, (β-diethylaminoethoxy)-phenyl group, potential untoward reactions regarding lens opacity or defects in cholesterol metabolism have been carefully looked for but have not been found following use of clomiphene for short term treatment.

Progesterone and Related Compounds

Progesterone and more recently the synthetic progestational steroids have been commonly used for therapy of anovulatory patients.[49] In most instances, this is designed as substitutional therapy to provoke progestational changes in the endometrium and more physiologic bleeding. The hope is often expressed that with the cyclic use of progestational agents the pituitary will be trained to a cyclic pattern or that there will be a rebound release of stored gonadotropins following cessation of therapy. This requires acceptance of the concept of inhibition of release of gonadotropin as the primary mechanism of the antiovulatory action of progestational compounds. Attempts to explain the antifertility effects of these drugs have provided us with some information on their effects on gonadotropin production and release. In laboratory animals the inhibition of release of pituitary gonadotropins by natural and synthetic progestational agents can be demonstrated by a variety of techniques.[*] In humans, however, the excretion of total urinary gonadotropins is not regularly suppressed although suppression of LH seems to be more consistent.[†] There is also some evidence that these agents may prevent conception through a direct effect on ovarian steroid synthesis or on cervical and endometrial epithelia.[‡] Recent reports of a higher incidence of multiple pregnancy occurring after discontinuation of progestational agent contraception would tend to support the theory that following cessation of progestational agent therapy there is release of an increased amount of gonadotropin.[105] There are several reports of an increased pregnancy rate after treatment of infertile patients with these drugs.[49,81,102]

In lower animals progesterone is known to facilitate ovulation under certain experimental conditions and to inhibit ovulation under others.[§] Relatively small quantities of progesterone are secreted by the ovary before rupture of the follicle, but the importance of this in the mechanism of ovulation in humans is undetermined.[110] Progesterone itself given either intramuscularly or intravenously has been reported to induce ovulation in humans, but this method has never become popular.[49]

Direct Methods of Ovulation Induction

Human Chorionic Gonadotropin

Human chorionic gonadotropin (HCG) derived from the urine of pregnant women is relatively easy to obtain in large quantities, is available in standard potencies and is devoid of clinically significant toxicity. Attempts to induce ovulation with HCG have been made for many years.[10,26,51,98] Although in Europe reports of its use continue to appear, it has never been widely used in the United States for this purpose. Greater success following intravenous use has been reported recently.[52]

As was previously mentioned, if patients are first treated with other gonadotropins which manifest follicle stimulating properties, administration of HCG will result in ovulation. In intact laboratory rodents, HCG, acting in synergy with endogenous follicle stimulating gonadotropins, will cause ovulation and corpus luteum formation. In hypophysectomized animals, however, it will not cause ovulation but only luteinization of the theca cells of the ovary.[33,103a] Thus, in man and in experimental animals, the principal action of HCG seems to be similar to that of LH. Its success in the induction of ovulation, therefore, depends on follicular development by endogenous or exogenous gonadotropins.

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[*] Reference Nos. 4, 44, 64, 70, 77, 78.

[†] Reference Nos. 7, 8, 37, 57, 63, 82, 100.

[‡] Reference Nos. 14, 17, 22, 57, 59, 111.

[§] Reference Nos. 18, 21, 31, 44, 49, 64, 65, 79, 89.

HCG also has actions similar to luteotropic hormone (LTH) since administration of HCG to women following ovulation will delay the onset of menstruation, presumably by prolonging the activity of the corpus luteum. Its use in the treatment of deficient luteal phase is on this basis, although there is considerable doubt that LTH is necessary in the human during the normal cycle.

Gonadotropins of Animal Origin

Species specificity of gonadotropic hormones has delayed progress in the use of these hormones for the induction of ovulation in women. Although gonadotropins from other species are able to induce ovulation in humans, antibodies soon develop to these gonadotropins,[74] resulting in refractoriness to treatment and, in some instances, in cross reactions with human gonadotropins so that, in theory, endogenous gonadotropins are inactivated. The gonadotropin produced by the horse placenta is not readily excreted in the urine but may be obtained from the serum—pregnant mare serum gonadotropin (PMS). PMS has been used successfully for the induction of ovulation in the human—sometimes alone, but more often in combination with HCG.[51,98] Its use has been recommended as a diagnostic test of ovarian responsiveness before use of human gonadotropins.[93]

A second serious hazard to the use of PMS, perhaps related to its prolonged duration of action and poor urinary excretion, is the difficulty in establishing an effective dose. There are many reports in the European literature of massive overstimulation of the ovaries following sequential use of PMS and HCG,[112] leading to hemorrhagic corpus luteum cysts, hemoperitoneum and, in several cases, death.

Gonadotropins derived from the pituitary glands of common slaughterhouse animals have been tried in humans[41,51,54,62] and in other primates[45] with some success. Although species specificity of response is not as great for gonadotropins as for growth hormone, it is much greater than for ACTH or insulin and the development of antibodies has been a serious problem. At present the difference in biologic activity and the risk of antibody formation prevent widespread application of even the most purified animal pituitary hormone preparation to the problem of induction of ovulation in the human.

Pituitary Gonadotropins of Human Origin

Development of methods for the isolation and purification of gonadotropins of human origin in quantities sufficient to treat substantial numbers of patients is a milestone in gynecologic endocrinology. It is a significant advance which holds promise of immediate clinical applicability for induction of ovulation in patients previously without hope of fertility. Many problems, however, are still to be met. Whatever the source of gonadotropins, the degree of purification and the resulting action in the recipient varies from batch to batch.[85] With specific bioassays as a guide, it may be possible to produce a product of consistent and predictable potency, much as the brewer or vintner blends natural products from varied sources to produce a consistent blend.

Induction of ovulation in humans by administration of gonadotropins of pituitary origin was first reported by Gemzell in 1958.[26] His preliminary work was confirmed in the United States by Buxton and co-workers in 1960.[10] Induction of ovulation was accomplished using HCG as a substitute for LH since the pituitary extracts had mainly FSH activity. Pituitary glands from 10 subjects are needed to yield sufficient gonadotropins to treat one patient for one cycle. This remains the major practical handicap to the wide employment of gonadotropins of human pituitary origin. It is of interest in this regard that the United States Public Health Service and the Veterans Administration have begun studies in which pituitary tissue obtained from a large number of hospitals is extracted and purified.[19] Members of this study group have reported methods by which several of the clinically useful pituitary proteins are extracted from fresh pituitary glands or from glands from embalmed bodies.

It is relatively easy to isolate chorionic gonadotropin from the urine of pregnant women, the concentration of gonadotropin being high during pregnancy. Pituitary gonadotropins are excreted in low concentration in urine even in castrate or menopausal subjects. Therefore, the volume of urine required is large and the extraction and purification steps are more complex.

Three preparations of urinary gonadotropins have been obtained in sufficient quantity and of sufficient purity to be evaluated in clinical practice for the induction of ovulation.[13,15,59] One of these, the previously mentioned Pergonal, a preparation of urinary origin particularly rich in FSH activity, is under clinical investigation in the United States under the direction of Cutter Laboratories, Berkeley. The source is post-menopausal women, reportedly retired Italian nuns. The gonadotropins are extracted from the pooled urine by kaolin-acetone precipitation, concentrated and purified by several steps in which the crude precipitate is dissolved in various solvents, reprecipitated, absorbed on a Permutit® column, eluted and finally filtered through Sephadex® and freeze-dried.[16] In this state it is stable for long periods of time. Pergonal has been under clinical investigation for the past five years and has been shown to be a highly effective FSH preparation. The response to Pergonal is not decreased after repeated treatment,[83] and development of precipitating antibodies has not been demonstrated in humans and would not be anticipated. Antisera to Pergonal and other human gonadotropins, however, have been developed in laboratory animals in which they are foreign proteins.[58,66,109]

The greatest hazard of gonadotropin therapy appears to be unpredictable sensitivity or, if you will, overdosage. Enlargement of the ovaries is common and, perhaps, desirable since the pregnancy rate is higher in patients with ovarian enlargement.[26] The incidence of multiple pregnancies is greatly increased, indicating development and release of ova from many follicles. In the popular press in 1964 there have been reports of the birth of several sets of quadruplets and the premature delivery of septuplets following induction of ovulation with gonadotropins. Massive ovarian enlargement may occur from the simultaneous development of many follicles, and there have been occasional reports of ascites and hydrothorax or of rupture of the cysts requiring operative intervention.[26,29,75] Problems of dosage adjustment are currently under investigation. It has been suggested that patients be tested first with HCG alone and that those few who respond not be treated with other gonadotropins. Caution is advised also in treating patients with enlarged or cystic ovaries (Stein-Leventhal syndrome) as it is said that they are prone to development of cystic enlargement of the ovaries after gonadotropin administration. The response to human gonadotropins seems to be related to the potency of the preparation in terms of FSH, as measured by the augmentation test, rather than in terms of total gonadotropins, as measured by rat uterine or ovarian weight assays.

The preferred methods of treatment with urinary gonadotropins involve administration of the equivalent of 500 to 1,000 "units" of FSH (approximately equivalent to 120 mg of the international reference preparation, HMG 20-A) daily for eight to ten days, followed, within the next few days, by the administration of a large dose of chorionic gonadotropin such as a single injection of 10,000 to 15,000 international units or several daily injections of 3,000 to 5,000 international units each. With preparations containing little LH activity ovulation will usually not occur in the absence of HCG. Modifications of this schedule have been used in an attempt to mimic various ideas of secretory patterns of FSH and LH.[23] Following ovulation, further administration of HCG is not necessary even in women who have had hypophysectomy. The biologic half-life of HCG is such that it is excreted within a few days, implying that humans do not need luteotropic hormone activity for support of the corpus luteum after the first few days.

In Table 3 are listed representative reports of the use of human gonadotropins for the induction of ovulation. Because in several references the information was not clearly stated, the table does not include the percentages of patients or cycles in which attempts to stimulate ovulation were successful. Comparisons with other methods of treatment should not be made since many of the patients treated with gonadotropins are those with long-term amenorrhea which was not benefited by treatment with other agents. Several of the pa-

TABLE 3.—*Results of Treatment of Anovulation with Human Gonadotropins as Reported by Various Investigators*

Author	*Source of Gonadotropins*	*Patients*	*Number Pregnant*
Gemzell[26]	Pituitary	35	18
Buxton[10]	Pituitary	11	3
Meares[67]	Pituitary	3	0
Bettendorf[3]	Pituitary	19	0
Crooke[13]	Pituitary and urinary	9	6
Diczfalusy[15]	Pituitary and urinary	6	2
Rosemberg[84]	Urinary	11	1
Paseto[75]	Urinary	14	2

tients successfully treated had severe pituitary deficiency. In addition several of the reports deal with trials of varying dosage schedules of new preparations. Once a suitable schedule was established, ovulation could be induced in the majority of patients.

The Future

What lies ahead in the field of ovulation induction? Several possibilities are suggested by recent work in laboratory animals. At present they are purely speculative.

A gonadotropin-releasing factor of relatively simple chemical structure but specific physiologic activity has been obtained from the hypothalamus. Purification or synthesis of such a compound might provide another direct means of ovulation induction in the human by regulation of the release of LH.[64]

The amino acid sequences of ACTH and related pituitary protein hormones have been identified and several physiologically active polypeptides, representing parts of the molecule, have been synthesized. The methods used in this achievement are being directed to the study of the gonadotropins and other pituitary hormones with a goal of eventual synthesis of the hormones to provide a practical source sufficient to meet the demand. Perhaps minor alterations of the protein hormones derived from animal pituitary glands could be accomplished with maintenance of physiological activity but loss of antigenicity.

A gonadotropin inhibiting substance has been identified in urine and found to vary in concentration under various conditions.[97] The role this factor plays in the physiology of the reproductive cycle and the pathophysiology of some types of anovulation is still under investigation. It does not seem overly presumptive to expect the development of competitive antagonists or antibodies to this substance which might be of use in the induction of ovulation.

Research in the neurophysiologic control of LH release has yielded information about specific centers in the hypothalamus which, upon electrical stimulation, produce the gonadotropin releasing factor mentioned above and result in the release of LH into the circulation.[21,64,89] It has been suggested that, even in animals other than those (such as the rabbit) which ovulate only after copulation, there may be reflexes involving these centers which can be initiated by external stimulation and result in the release of gonadotropins. How far into the world of science fiction do we go to envision the induction of ovulation by manipulation or electrical stimulation?

Development of a safe, cheap, consistently effective, oral preparation for the induction of ovulation by whatever mechanism would be of considerable interest and would allow the use of this therapy for conditions in which fertility is not a consideration and in which substitutional therapy with progestational agents is now employed. Moreover, such an agent would be of considerable interest to the estimated five million young Catholic couples in the United States. Many of them find the use of the rhythm system of contraception ineffective or impractical because of irregular cycles and difficulty in accurately determining the time of ovulation.[30] Since the Roman Catholic Church has not, as yet, authoritatively approved for use by its members the ovulation-suppression or mechanical methods of contraception, many women who do utilize one of these methods are disturbed by the side effect of reduced tranquility which accompanies the reduced fertility. It seems reasonable, at this moment, that a method utilizing ovulation induction for improving the effectiveness of the rhythm system would be acceptable to at least a large segment of Catholic theologians.

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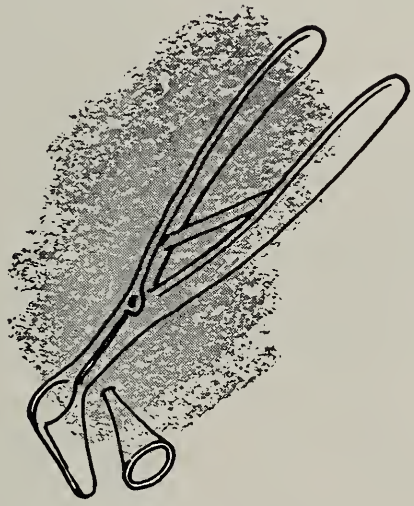

CASE REPORTS

Nausea as the Chief Complaint in Thyrotoxicosis

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IT IS WELL KNOWN that hyperthyroidism, especially in older persons, may be protean in its clinical manifestations. The outstanding symptoms range from nervousness, hyperhidrosis, weakness and fatigue, to palpitation, loss of weight, diarrhea and shortness of breath. I recently observed a patient in whom nausea was the most significant symptom—nausea that was both persistent and intractable. No previous report of such a case was found in a review of the literature, although Williams[1] reported anorexia in 9 per cent of 274 patients with thyrotoxicosis and said that occasionally nausea and vomiting are associated with this.

Report of a Case

The patient, a 56-year-old jeweler, had been under my care for four years when, on January 8, 1963, he arrived at the office complaining of constant nausea, without vomiting, for a period of two weeks. This was his main symptom, and other symptoms were elicited only after careful questioning. He had lost 11 pounds in the preceding six weeks. As he was taking digitalis, he was questioned regarding bradycardia and xanthopsia, but he said that he had experienced neither. He did mention an occasional "swimming" visual sensation and said that he had been having much more angina than usual, even, for example, if he merely got out of bed during the night. Also he remarked that a slight reduction in the room temperature would bring on angina. He had not had abdominal pain, but he spoke of three to four daily bowel movements, of normal consistency, occurring one or two hours after eating. This symptom had been present for almost a year. The patient said that he was taking 12 to 15 nitroglycerine tablets a day, but even so had to do things more slowly than ever before. He said he was somewhat more nervous, tense and jittery than previously. He had had occasional heavy sweats over the past six weeks and itching of the skin for four to five months.

The patient had had severe myocardial infarction in 1951. In 1960 he was discovered to have chronic cholecystitis with cholelithiasis, and in 1961 biliary colic developed, necessitating cholecystectomy. He did well, but in March of 1962 biliary colic recurred, then cholangitis developed and a second operation was done in May of 1962. At that time a soft stone was removed from the common duct. In November of 1962 symptoms and signs of mild congestive failure developed and digitalization was carried out with excellent results.

Accordingly, at the time the patient was examined in January of 1963, a number of possible reasons for nausea had to be considered: digitalis intoxication, hepatic congestion, recurrent biliary tract disease and hepatitis, as well as other less likely causes of nausea.

The pulse rate was 90 to 95, the blood pressure 150/74 mm of mercury and the patient looked pallid and cachectic. Abnormalities noted on general physical examination were a Grade II apical systolic blowing murmur and slight symmetrical enlargement of the thyroid gland. Because of the general appearance of the patient, the history of

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Submitted October 26, 1964.

sweating and the increased nitroglycerin requirement, a blood specimen was taken for determination of protein-bound iodine and uptake of radioactive triiodothyronine and the patient was admitted to hospital. Intensive efforts to relieve the nausea with symptomatic treatment were unsuccessful. An electrocardiogram in the office before admission did not show changes characteristic of digitalis intoxication. An x-ray film of the chest in the hospital was normal except for calcific plaques in the aortic arch. An upper gastrointestinal tract series was normal except for slight irregularity in the gastric antrum and some indentation of the post-bulbar duodenum. No abnormalities were observed in barium enema studies or in sigmoidoscopic examination. Results of a complete blood count and urinalysis were within normal range. Serum cholesterol was 107 mg, fasting glucose 108 mg and urea nitrogen 22.5 mg per 100 ml. Thymol turbidity was 4.0 units, bromsulfalein retention less than 2 per cent, lactic dehydrogenase 365 units, sodium 148 mEq and potassium 5.6 mEq per liter, zinc turbidity 6 units, and prothrombin time 17 seconds with a control of 16 seconds. Shortly after the patient was admitted, a telephone report was received that the protein-bound iodine content of the specimen of blood taken just before admittance to hospital was 14 micrograms per 100 ml and the uptake of radioactive triidothyronine was 36 per cent. No additional abnormalities were elicited in the course of examination. On January 16, radioactive iodine uptake in 24 hours was 88.7 per cent, and on January 23 the serum protein-bound iodine was 13.7 micrograms per 100 ml.

The patient was referred to a radiotherapist who recommended administration of propylthiouracil for three weeks, then a therapeutic dose of I^{131}.* This was begun, and when the patient was seen on February 15, after three weeks of treatment with propylthiouracil, angina had decreased, his appetite had improved, and bowel movements had decreased in frequency. He said that he had noticed a decrease in nausea within 24 hours after starting to take propylthiouracil, and complete disappearance of this symptom and of angina after another 48 hours. Then just before administration of the therapeutic dose of I^{131}, he was advised to discontinue propylthiouracil temporarily. Angina recurred almost immediately and within three or four days he again had chronic, moderately severe intractable nausea. Propylthiouracil was resumed but it had to be discontinued when arthralgia developed, and once more nausea recurred and angina increased. Administration of methimazole (Tapazole®) relieved the nausea and angina, and after the therapeutic dose of I^{131} was given the patient recovered and remained symptom-free.

Discussion

Although interesting because of the rather occult nature of hyperthyroidism in this patient and the presence of multiple other problems, the main point of interest in this case must be the striking correlation of chronic nausea with hyperthyroidism, the relief of this symptom when thyrotoxicosis came under control and recurrence of the symptom whenever treatment was interrupted. This is a rather rare manifestation of hyperthyroidism, but an important one to remember.

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*Sheldon Margen, M.D., carried out the radioactive tracer studies and the therapeutic administration of iodine 131.

Exogenous Adrenal Suppression in Infancy

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THE ABILITY of the normal adrenal gland to survive long periods of suppression has been investigated previously.[1] Not to my knowledge, however, have the consequences of suppression of the neonatal adrenal gland for prolonged periods been analyzed. An amazing set of circumstances gave me an opportunity to study adrenal gland suppression in an infant and the results contribute to the known facts concerning the ability of the adrenal-pituitary axis to withstand prolonged suppression.

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Submitted September 30, 1964.

TABLE 1.—*Results of Laboratory Studies of Plasma and Urinary Contents Associated with Intermittent Hormonal Therapy*

	Hormonal Therapy		Urine					
Date	*Cortisone (daily)*	*ACTH*	*Total Volume (ml)*	*Creatinine (mg/100 ml)*	*17-hydroxycorticoids** (mg/24 hours)	*17-ketosteroids* (mg/24 hours)	*Pregnanetriol* (mg/24 hours)	*Plasma 17 OHCS (µgm/100 ml)*
December 1963—								
9	10 mg		470	148	5.4	1.1	0.04	......
15	10 mg	5 U q 12 hours × 5 days	960	......	5.3	1.1	0.4	......
January 1964—								
5	10 mg	15 U q 2 days × 30 days	450	171	4.6	1.0	0.4	......
8	Dexamethasone 0.33 mg (1 day)	15 U q 2 days × 33 days	405	191	5.1	1.0	1.0	......
31	0 × 2 days	0 × 3 weeks	570	108	2.1	0.0	....	......
February—								
2	0 × 7 days	0 × 3 weeks	830	......	2.9	0.2	0.1	......
1	8 a.m.		......	......	....	....	....	17.2
1	4 p.m.		......	......	....	....	....	7.0

*Porter-Silber chromagens in the urine.

Report of a Case

The patient, a 21-month-old white boy, was the fourth of six children. Four siblings were living and well. The fifth died at eight weeks following severe gastroenteritis (a diagnosis of salt-losing adrenogenital syndrome was made on the basis of biochemical evidence and confirmed at autopsy). A maternal cousin, aged 12, also had congenital virilizing adrenal hyperplasia.

He was born in India, far removed from modern laboratory facilities. When he was ten days of age, vomiting, weight loss, weakness and lethargy developed. The local physician, aware of the family history, made a presumptive diagnosis of salt-losing adrenal hyperplasia and treated the infant with cortisone, desoxycorticosterone acetate and the addition of salt to the diet. No stigmata of virilization were noted at the onset of therapy. The child thrived on this regimen, with normal rate of growth, weight increment and mental achievement. At seven months of age, periorbital and distal extremity edema was noted and salt addition was discontinued. Minor infections did not cause undue difficulty and the desoxycorticosterone acetate was reduced and finally discontinued when the patient was 16 months of age. Cortisone therapy was increased gradually by adding approximately 5 mg to the daily dose every three months until, at the time I first saw him, he was receiving 37.5 mg daily in divided doses. No signs or symptoms of Addisonian crisis or Cushing's syndrome have ever been observed. The patient was admitted to H. C. Moffitt Hospital at 21 months for evaluation of adrenal status.

On physical examination he appeared well developed, well nourished, alert, active and intelligent, and there was no evidence of acute or chronic disease. His height (85.5 cm) and weight (29 kg) approximated the 50th percentile for his chronological age. Blood pressure was 115/75 mm of mercury, the pulse rate 100 and respirations 22 per minute. Specifically noted was the absence of moon face, centripetal fat distribution, buffalo hump, striae, acne, hirsutism, sexual hair, phallic enlargement, abnormal rugation of the scrotum, wasting and neurological abnormality.

The results of laboratory studies of serum and urinary contents are shown in Tables 1 and 2.

Results of routine examination of the blood were as follows: Hemoglobin, 13.2 gm per 100 ml, hematocrit 40 per cent; leukocytes 7,000 per cu mm—40 per cent polymorphonuclear cells, 4 per cent eosinophils, lymphocytes 52, monocytes 2. The specific gravity of the urine was 1.015, the pH 5.5. There was no evidence of sugar, acetone or albumin, and the sediment was within normal limits.

Roentgenograms of the skeleton showed a bone age of 18 months at a chronological age of 21 months. An intravenous pyelogram and renotomograms showed no abnormalities and retrograde renal air insufflation showed no evidence of adrenal tumor.

During a three-month period of observation, reduction of cortisone from 37.5 mg daily to 10 mg daily had no noticeable clinical or biochemical effect. Stimulation with ACTH three times weekly for one month was similarly accompanied by no change. Cessation of all medication did not cause any adverse signs or symptoms during a

TABLE 2.—*Laboratory Data on Serum and Urinary Contents Associated with Hormonal Therapy*

Date 1964	*Treatment*	*K*	*Na*	*Cl*		*Creatinine*	*Ca*	*Total Protein*
		mEq/Liter			*CO_2*	*(mg/100 ml)*		*(gm/100 ml)*
SERUM:								
January—								
8	10 mg cortisone + 15 U ACTH daily	5.0	137	......	......	....	......	....
30	0 × 2 days	5.0	141	114	......	0.5	......	....
February—								
4	0 × 7 days	5.2	135	106.5	21.8	0.6	10.7	7.2
URINE:								
January—								
7	10 mg cortisone + 15 U ACTH (450 ml)	33	36	......	......	....	......	....
10	10 mg cortisone + 15 U ACTH (405 ml) sp. grav. 1.019	24.3	49.4	62.0	......	68	......	....

ten-day period and the moderate stress of the retroperitoneal air insufflation study was well tolerated.

Comment

The degree of suppression achieved during the 21 months of life in the patient in the present case is unknown, but the absence of any features of Cushing's syndrome or growth failure suggests that suppression might not have been complete. Nevertheless, the dosage of cortisone was always greater than the 15 to 25 mg per square meter of body surface which is assumed to be the average adrenal secretory rate. It thus seems reasonable that a considerable degree of suppression was present at all times.

The relatively high values of 17-hydroxycorticosteroids (Table 1) probably represent the combined total of the degradation products of endogenously secreted cortisol and the exogenous 10 mg of cortisone that the patient was then receiving. (Approximately 30 per cent of exogenously administered cortisone is excreted in the urine as Porter-Silber chromogens.)

The one elevated level of urinary 17-hydroxycorticosteroids while the patient was receiving dexamethasone is difficult to understand. Cessation of therapy demonstrated the low normal level of urinary 17-hydroxycorticosteroids produced endogenously. Unfortunately, an ACTH stimulation test was not attempted at that time. However, the demonstrable diurnal variation of plasma cortisol levels within the normal range strongly suggests the preservation of pituitary ACTH secretion and the ability of the adrenal glands to respond. The capability of this system to respond to severe stress was not tested.

There is no evidence to support the diagnosis of adrenal adenomata or adrenal virilizing hyperplasia in this patient. Steroid supplementation was advised for any acute stress during the year following the time the patient was under observation.

Continuous suppression of the adrenal gland of a boy baby for almost two years beginning soon after birth did not result in irreversible disuse-atrophy of the gland or in permanent loss of pituitary ACTH secretion.

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Persistent Mediastinal Hematoma

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INTRAPULMONARY HEMATOMA subsequent to thoracic trauma is a well recognized and documented entity. Localized and circumscribed collections of blood are often seen roentgenographically following closed-chest injury. In some instances such hematomas have been mistaken for intrapulmonary neoplasms or granulomas. As a consequence of the usual shrinkage and eventual

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Submitted August 19, 1964.

disappearance of such shadows, they have earned the sobriquet *vanishing lung tumors*.

Mediastinal hematoma formation after nonpenetrating injury is less common, as hemorrhage produced by involvement of the aorta and its major branches and the large veins is usually exsanguinating or is terminated by primary repair.[12] In a review of 2,811 thoracic injuries of the Korean War, Valle[12] noted that in 117 of them the mediastinum was involved but in none of these did a discernible hematoma form. The first case of mediastinal hematoma reported in the literature followed a grenade blast during the First World War[13] and sporadic reports have appeared since. The source of the bleeding has been problematical in these cases, but most of the investigators have expressed belief that it originates in the rupture of small veins in the mediastinum.

In the majority of these cases no specific treatment was given and the progress of the lesion was observed by serial roentgenograms. Most of the hematomas disappeared in from two to twenty-four weeks. Williams[13] reported an average disappearance time of 7.3 weeks.

Cote[2] reported a case in which resection of the hematoma was carried out 14 weeks after diagnosis. It had enlarged slowly during this time and was firmly adherent to the pleura and pericardium.

Two cases of "spontaneous" superior mediastinal hemorrhage with hematoma formation were reported by Epstein.[4] The tumors disappeared without treatment within six weeks.

In 1949 Harrington[5] included two organized calcareous hematomas among 168 cases of intrathoracic, extrapulmonary tumors, but did not discuss them further. Laipply,[6] in his classification of cysts and cystic tumors of the mediastinum, listed cystic hematomas as a subdivision of his "acquired" group. He did not discover any in a series of cases that he reported, however, nor did Bradford and his associates,[1] who utilized Laipply's classification. Indeed, none were reported among nearly 2,000 mediastinal cysts and tumors in several excellent series. Thompson[11] in an earlier, extensive review of the literature found none, and no mention is made of hematomas in two collections[7,8] of reports of rare and uncommon mediastinal tumors.

Report of a Case

The patient, a 49-year-old woman, entered the hospital on September 24, 1963, preparatory to excisional biopsy of a nodule in the left breast. (This was carried out, and the excised breast tissue was reported by the pathologist to show cystic hyperplasia.) A routine preoperative x-ray film of the chest (Figure 1) showed a large mediastinal mass that displaced the trachea slightly to the left and depressed the right main bronchus. A right lateral film showed the lesion to lie in the mid-portion of the superior mediastinum. Except for the nodule in the left breast no abnormalities were noted on physical examination and on auscultation of the chest. Results of routine laboratory tests were within normal limits. The patient said she had no symptoms related to the chest or the respiratory, cardiovascular or gastrointestinal systems.

Tomograms showed calcium-like densities in the periphery of the lesion, and in some sections there were small areas of radiolucency. Aortographic examination demonstrated the relation of the mass to the aortic arch. Inquiries were made about any previous thoracic films that might be reviewed, but none could be found. As teratoid tumor was suspected, thoracotomy was carried out. A right posterolateral opening was made and after some apical adhesions were freed, the mass was seen to be widely and firmly adherent to the superior vena cava, the ascending aorta, the pericardium, the right upper lobe of the lung, the trachea and both main bronchi. With considerable difficulty the mass was freed without sacrifice of any of the involved structures except the azygos vein, which appeared to enter directly into the mass and lose its identity. Proximal and distal ligatures were necessary to free the tumor in this area.

When the mass was opened, approximately two

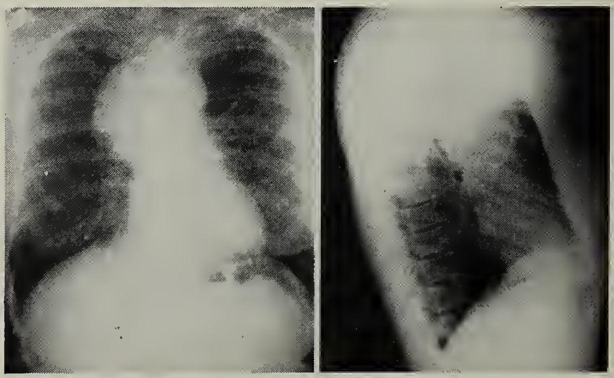

Figure 1.—*Left*, film shows large mediastinal mass displacing trachea to the left and depressing the right main bronchus. *Right*, the right lateral view shows the lesion at the mid-portion of the superior mediastinum.

hundred milliliters of thick, yellow fluid was removed, leaving a thick, shaggy, inelastic wall and innumerable yellowish concretions. The fluid contained degradation products of hemoglobin and the wall was composed of sclerotic, collagenous connective tissue. Careful sectioning of all tissue failed to reveal any suggestion of teratoid elements. Hemosiderin pigment was widespread. No foreign material was seen and the entire mass appeared to consist of a large, organized hematoma (Figure 2) with massive deposition of cholesterol.

The patient was able to return home a week after operation and thereafter remained well.

On further questioning later, the patient remembered that in an automobile accident approximately three years before she had been struck over the sternum. For several weeks afterward she had had moderate chest pain and painful cough. No x-ray films were taken at that time. A report of a routine x-ray film of the chest taken eight years previously was also discovered subsequently. The film had been destroyed, but the radiologist had reported clear lung fields, except for tiny areas of calcification, and no mediastinal abnormalities.

There are many extensive and detailed reviews of mediastinal cysts and tumors, which is a measure of the success of mass radiographic screening programs in bringing these often asymptomatic lesions to light. Such lesions are of great variety; as many as 26 different types have been distinguished in a single series.[9] Essentially normal variations may simulate abnormal masses in this location.[10] Careful analysis of large numbers of cases has delineated diagnostic possibilities, largely on the basis of geographic locus[3] but such boundaries are often breached.

The incidence of malignant change reported in various series of cases of mediastinal tumors varies from less than 10 per cent to more than 50 per cent, largely reflecting the inconstant inclusion of lymphomas and certain benign cysts. The overall figures would suggest that 15 to 25 per cent of "problem" mediastinal tumors will prove to be malignant. Most importantly, in all the major groups, with the exception of the endodermal and pericardial cysts, there are some malignant lesions. The uncertain nature of the roentgenographic shadows and the fact that usually the tumors can be removed without causing major pathophysiologic changes dictate a policy of thoracotomy and resection. While the great majority of mediastinal hematomas will disappear spontaneously and without consequence, careful, continued observation to that point would seem advisable.

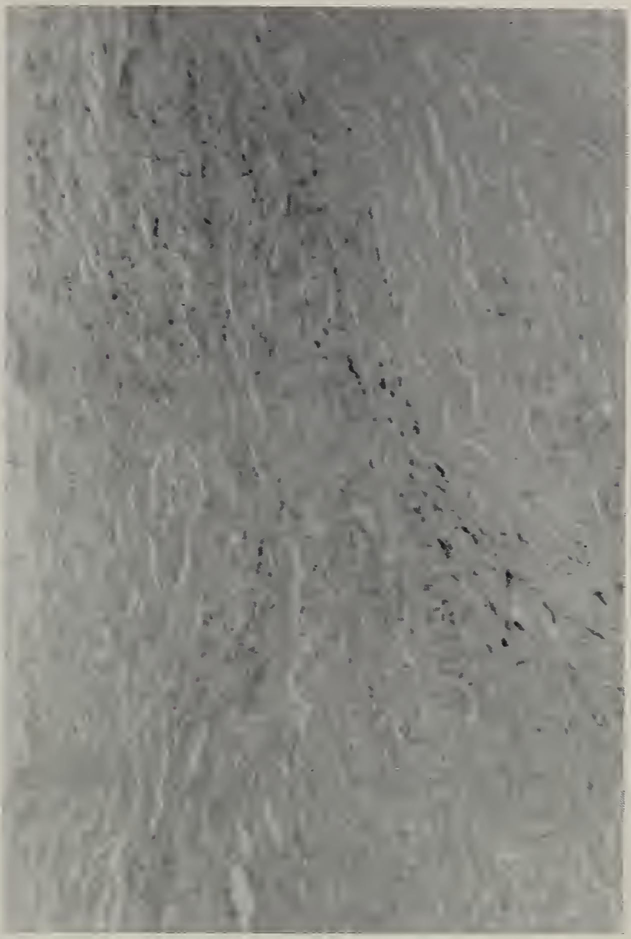

Figure 2.—Section from mass (×150), an organized hematoma, with heavy deposition of cholesterol.

Summary

A large, asymptomatic mediastinal mass in a 49-year-old woman was surgically removed because of suspicion of malignant change. It was found to be an old, calcified hematoma, probably secondary to a relatively minor chest injury three years previously. Persistence of a hematoma in this location is unusual but must be considered in the evaluation of such masses.

2 West Fern Avenue, Redlands, California 92373 (Moersch).

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Rupture of Cerebral Aneurysm During Angiography

CHING TUNG LIU, M.D.
Walnut Creek

ONE OF THE MOST feared complications of cerebral angiography is rupture of an aneurysm during the procedure. Reported cases have not been numerous.[1,2,3,4,5] The cause is not clear, but most authorities agree that the force of the injection does not play a role, nor does the nature of the dye. Wright[5] noted that in three of his patients the aneurysm ruptured when the contralateral common carotid artery was being compressed during the procedure in order to obtain "cross filling." This led him to study the intra-arterial pressure in 100 arterial puncture procedures in 71 unselected patients. He found that prolonged manual compression of the contralateral common carotid artery caused a precipitate rise in the intracranial intra-arterial pressure which could account for the rupture of the intracranial aneurysm. The following is a case in point.

Report of a Case

A 23-year-old man had sudden onset of headache on July 2, 1963, and spinal fluid aspirated that evening contained blood. There were no localizing neurological signs. Three days later right common carotid showed an aneurysm at the bifurcation of the posterior communicating artery. As the films were not satisfactory, angiograms were made again on July 8 and better delineation of the aneurysmal sac was obtained (Figure 1). Meanwhile, the spinal fluid had cleared up and the patient was improving clinically. On the tenth day after the onset of headache, an open angiogram was made of the left carotid artery under local anesthesia to complete the study and no abnormalities were seen in the vessels of the left hemisphere. Then as the puncture wound in the left common carotid artery was being compressed to stop bleeding, the patient suddenly shouted, "It's hurting on the right side." Within seconds the pain became generalized and he lapsed into coma immediately. We assumed that the aneurysm must have ruptured again and recognized that the prognosis was grave. In desperation, we decided to ligate the right common carotid artery. The incision on the left side of the neck was rapidly closed. The right common carotid artery was exposed and a Salibi-Selverstone clamp was applied with the arms of the clamp partially closed so that the diameter of the common carotid artery was

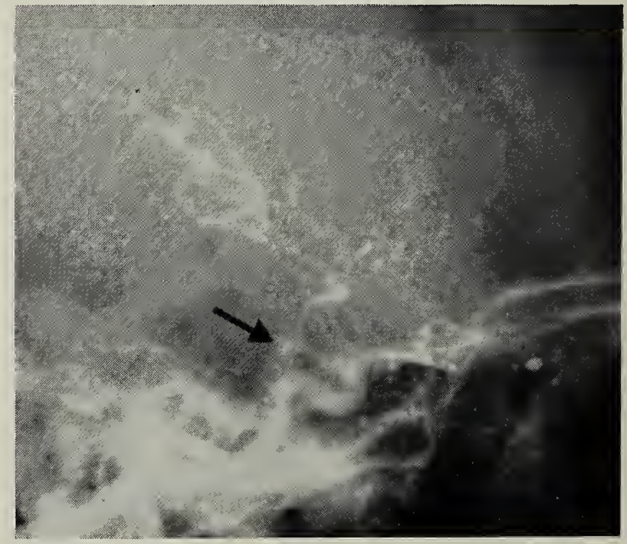

Figure 1.—Preoperative arteriogram. A "berry" aneurysm is shown arising from the internal carotid artery right where the posterior communicating artery originates. Note vasospasm distal to aneurysm. Other small round opacities are residual Pantopaque from previous myelogram for lumbar disc.

Submitted December 31, 1964.

reduced by half. To our amazement, the patient gradually regained consciousness over a period of two hours. Spinal fluid aspirated at that time was grossly bloody. Over the next 24 hours the Salibi-Selverstone clamp was completely occluded without incident. The patient made a slow recovery with no neurological deficit except for slow mentation and forgetfulness.

Seven weeks later an open arteriogram showed the aneurysmal sac to be smaller than before and the posterior communicating artery was more clearly seen (Figure 2). At last report, a year after the first hemorrhage, the patient was working at his former job as a carpenter.

Discussion

Often when an aneurysm has been demonstrated on one side, a repeat injection is done and the opposite common carotid artery is intentionally compressed to obtain "cross filling." This was the case in three patients reported upon by Wright.[5] In the case reported by Abbott and coworkers[1] the right common carotid artery was being compressed during injection to obtain retrograde vertebral filling, but an unsuspected aneurysm of the opposite posterior communicating artery ruptured. There may be other unknown factors leading to aneurysmal rupture. For instance, in the cases reported by Jamieson[3] and Jenkinson and coworkers[4] the aneurysm was on the same side as the arterial puncture and immediate rupture was proven by the demonstration of extravasation of dye in the angiogram. There was no clear explanation for this complication. However, the studies made by Wright[5] showed that the changes in the intra-arterial pressure may range from no change to 30 mm of mercury, with an average rise of 10 mm after 30 seconds of compression of the opposite common carotid artery. We believe that the hypothesis proposed by Wright is a sound one and we support his warning to avoid any prolonged manual compression of the common carotid artery when an aneurysm has already been demonstrated on the opposite side.

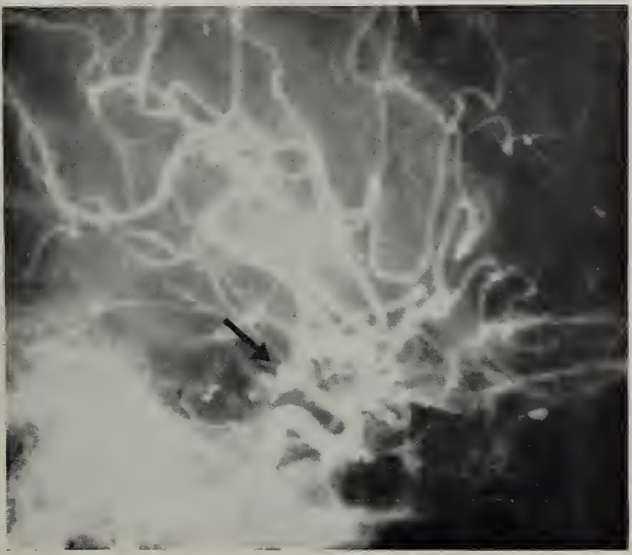

Figure 2.—Postoperative arteriogram seven weeks after ligation of common carotid artery. Aneurysmal sac is smaller than before and the posterior communicating artery is clearly visualized. Vasospasm has disappeared.

1855 San Miguel Drive, Walnut Creek, California 94598.

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EDITORIAL

Medicare 1965

SELDOM HAS A deliberative body in general session found it so necessary to dwell on one topic so extensively as did the House of Delegates of the American Medical Association at its regular meeting last month in New York.

While 76 resolutions were placed in the hopper of the House, nine dealt with the prospective effects of and the attitude to be taken toward HR 6675, the Medicare bill which has swept through the House of Representatives and the Finance Committee of the Senate and is widely known as the President's Number One objective in this session of the Congress.

Decisions on the bulk of the 76 resolutions introduced were arrived at with a minimum of controversy or even discussion. This held true even for seven resolutions arising from the report of the President's Commission on Heart Disease, Cancer and Stroke. As to the resolutions dealing with Medicare, however, discussions were long, heated and varied.

Underlying the entire discussion was a series of actions and declarations of principle taken in the past in anticipation of the potential enactment of this sweeping legislation. It must be said that the AMA House of Delegates has never taken a defeatist attitude on this form of the provision of medical services. It has never accepted the tenet that this is inevitable and that physicians should join it in an effort to guide it.

Rather, the AMA House of Delegates has consistently voted to use all possible ethical means to prevent the enactment of medicare legislation with its overtones of compulsion, control and dictatorship. In following this path the House has enacted statements of principles, chief among which are the Bauer Resolution adopted in June 1961, and a statement of principles for standards of health care programs approved in February of this year. These, together with Section 6 of the Principles of Medical Ethics, place the American Medical Association squarely on record that (1) the health of the patient comes first and (2) physicians are the best judges of what is best for the patient and the means to achieve the optimum results.

At last month's meeting these statements (see pages 57 and 60) were not a subject of debate but of interpretation as to the best means of conformation. Among the nine resolutions offered, some asked outright that non-participation in government programs of health care be adopted as the best method of opposition to a legislative proposal deemed inimical to the optimum standards of medical care. Others were more moderate in urging the maintenance of principles already adopted in order to protect the rights of the patient.

While these resolutions were under discussion, the grass roots were heard from in a number of telegrams and phone messages to members of the House of Delegates, some urging non-participation, some decrying the statements made by AMA's incoming president, Doctor James Z. Appel, in support of law and order, some offering subjective proposals.

Out of this welter of material the House of Delegates distilled a substitute resolution which the House approved. It reaffirmed earlier statements of principle, called for conferences to assure high quality medical care for patients, asked for the appointment of representative physicians to advisory committees in all federal health care programs, decried the compulsory inclusion of physicians under the Social Security laws and requested the appointment of a physician as an assistant secretary of the Department of Health, Education and Welfare. Notice of these enactments has already been sent to all members.

As to non-participation, the House of Delegates action places the individual physician squarely in the position of determining for himself whether or not he wishes to participate in the anticipated program.

Thus, for the time being at least, the AMA has adopted the blueprint for what a medical care program should be, in terms of quality of service. It has also declined to enter into a non-participation movement which is of dubious legal standing but has left its members free to make up their own minds, each in his own way and in conformity with his own methods and his own conscience.

Amid the atmosphere prevailing in the meeting itself and outside the headquarters hotel, this result appears most impressive.

Should further decisions be required of the AMA in meeting the challenge of governmental medical care programs, another meeting of the House of Delegates is scheduled to be held next November and the Board of Trustees is authorized to call a special meeting if the need is urgent.

California delegates occupied a number of reference committee and other official posts and acquitted themselves admirably before reference committees and on the floor of the House of Delegates. California members may well be proud of their elected representatives in providing leadership and strength in guiding the national body into sensible, practical and democratic paths.

RESOLUTION ON MEDICARE BILL

Following is the text of the resolution passed by the AMA House of Delegates with regard to HR 6675, the so-called Medicare Bill before the Congress of the United States:

Resolved, That the physicians of the United States of America pledge themselves to continue their search and activity, in whatever social environment may develop, to secure or to restore the freedom, high quality and availability of medical care which has been traditional in our country; and be it further

Resolved, That when the fate of the pending medicare legislation is determined, this House will review, in special session if necessary, the effect of the law and take whatever action is deemed necessary; and be it further

Resolved, That in keeping with the testimony before your Committee, and the expressed policies of this House, this action should in *no way* be interpreted as a change in Section 6 of the "Principles of Ethics" of the American Medical Association which plainly states: "A physician should not dispose of his services under terms or conditions which tend to interfere with or impair the free and complete exercise of his medical judgment and skill or tend to cause a deterioration of the quality of medical care"; and that this House of Delegates reaffirm the principles of the Bauer amendment adopted in 1961; and be it further

Resolved, that the House of Delegates reaffirm the nine principles for standards of health care programs as adopted by the House of Delegates in its special meeting February 7, 1965, and amended to read as follows:

"1. No person needing health care shall be denied such care because of the inability to pay for it.

"2. It is appropriate that government revenues be used to finance health care when other resources have been found to be inadequate.

"3. Every level of government, municipal, county, state and federal, should assume a responsible share in the financing of such programs.

"4. The health care provided by such programs should be adequate and should be equal to that available to those who can afford to pay.

"5. Maximum use should be made of voluntary prepayment and insurance mechanisms.

"6. Administration of such program should be the responsibility of the state government. Participating states should be required to meet adequate standards of administration in order to qualify for federal funds.

"7. Eligibility requirements for benefits should be fair, realistic, uncomplicated and practical.

"8. Any such health care programs should provide funds only, and not direct services.

"9. Funds for such programs may come from general tax revenues and not from social security taxes."

(See page 60 for further report of actions at AMA meeting.)

A Better Journal

Beginning with this issue, California Medicine is being printed in a slightly more expanded type face and on a whiter paper than we have used heretofore. Both changes are for the purpose of making our journal more attractive to the eye and easier to read. They are the latest in a series of physical improvements that were engendered by general recommendations from the Scientific Board to the Council and by specific proposals by the Committee on California Medicine of the Scientific Board. Changes in the cover design and in the styling of titles and page layout were made a year ago.

A request for the money needed for the better paper and the more readable type face that we begin using this month was readily endorsed by the Finance Committee, approved by the Council and voted by the House of Delegates at its meeting in March of this year. We believe that, over and above the factor of improved appearance, even a little gain in readability or relief of eyestrain, multiplied by the total number of our readers, makes this money well spent.

This little celebration of a culmination of graceful physical changes is not to be construed as reflecting a preoccupation with matters of dress, for the physical improvements have been brought about as deliberate complement and supplement to a more important development—a rising quality of material published in California Medicine. Through a growing if informal concert of effort by such forces as the Scientific Board, the Committee on California Medicine, members of medical school faculties, organized specialty groups, our own Editorial Board and individual physicians, our journal is getting access to better and better medical manuscripts. All these elements are serving as scouts for good material and as agents of good will.

One outstanding item of improvement in content is the series of review articles on latest progress in various fields of medical research and practice. These articles, which have been appearing monthly for more than a year, have brought a good deal of favorable comment from readers. This excellent feature brings with it an extra dividend: It not only attracts readers, it is fetching the attention of writers who are learning to think of California Medicine as a good medium for publication of important work.

Improved physical appearance, better scientific material and that hard to define but cogent factor, *esprit de corps,* are blending nicely to make California Medicine a more effective educational instrument for its own readers and a journal whose stature is recognized abroad. When the American Medical Writers Association, meeting last fall, named California Medicine the leading state medical journal of the year, we welcomed the distinction as one ray in the greater illumination of the leading state medical association which publishes it.

New Dean at Stanford

When faculty and students at Stanford University's School of Medicine take up the business of teaching and learning this fall, their work will be under the general direction of a new dean who was carefully selected for the job after diligent search for the right man by a committee of the faculty. He is Dr. Robert J. Glaser, whose background of experience and demonstrated ability in administration and teaching (see page 71) recommend him to the place he will now take as leader of one of California's outstanding medical schools.

We congratulate him on his new job and we wish him well in it. We welcome him to California.

The President's Page

ARE YOU KEEPING UP-TO-DATE?

Sir Joseph Lister, the great English surgeon, was keenly aware of the tremendous importance of postgraduate medical education to the busy—and often harried—practicing physician. He once summed it up for his students with this trenchant statement:

"You must always be students, learning and unlearning until your life's end, and if, gentlemen, you are not prepared to follow your profession in this spirit, I implore you to leave its ranks and betake yourselves to some third-class trade."

This was true in Sir Joseph's day and—because medical progress now is in its own jet age—it is doubly true today. Continuing your medical education is one of the most vital responsibilities you have, for the good of your patients and for your own professional good.

Most California physicians are meeting this responsibility. All studies show that they are attending postgraduate courses in unprecedented numbers—voluntarily and with considerable investment in time and money. This is strong evidence that the great majority of our physicians *are* lifelong students of medicine and that they intend to continue to provide the finest possible care for their patients.

The importance of continuing medical education has long been recognized by the California Medical Association. Our first Committee on Postgraduate Activities was appointed in 1934. Since that time, postgraduate education for physicians all over the county has grown from infancy to young adulthood—from a few scattered, loosely organized conferences to an enormous program accounting for millions of dollars and thousands of hours of time and effort.

The great expansion of knowledge has been accompanied by rapid expansion of medical postgraduate courses, radio and television programs and medical journals and publications—all designed to keep the physician abreast of the scientific revolution.

Since World War II, formal postgraduate departments have been organized in our California medical schools. The CMA has maintained close cooperation with them. Directors of continuing medical education in five of our medical schools serve as consulting members on the CMA's Committee on Continuing Medical Education.

In postgraduate institutes and circuit courses jointly sponsored by the CMA, county medical societies and the medical schools, we have tried to create a climate in which there will be more understanding and closer cooperation between teachers and practitioners. In attempting to act as a catalyst, we have publicized all postgraduate courses and medical meetings in the state by listing them in California Medicine and in *Medical Dates Bulletin.*

An accreditation program for continuing medical education courses is being developed by the American Medical Association's Council on Medical Education.

We are never satisfied with the status quo. We seek better quality, more efficient methods, keener evaluation techniques of the effects of continuing education on the practice of medicine, a more secure financial basis for these departments in medical schools, studies of the actual needs of our physicians and ways to encourage more active participation by more physicians.

The CMA's Committee on Continuing Medical Education, with full cooperation of the medical schools, is studying all these problems. It has embarked on some new projects intended to help solve them.

One is a thorough study of physicians' needs in continuing education, including a study of how physicians apply what they learn after attending postgraduate courses. Another is a new bi-monthly continuing education page in CALIFORNIA MEDICINE devoted to all facets of the program. Third, a four-page insert devoted to postgraduate education will appear annually, starting this fall, in CMA *News*. Fourth, an information center and postgraduate clearing house is being set up through which all data on every postgraduate course and medical meeting in the state will be made easily available to all physicians, medical schools and medical organizations.

I urge each of you to make the fullest possible use of your postgraduate education opportunities. Make known your requests. They will be answered. Choose carefully, from the rich feast available, those courses that will be most useful to you and to your patients. The courses are there for the asking. It's up to you to use them.

Ralph C. Teall

ACTIONS AT AMA MEETING

THE FOLLOWING REPORT of actions taken by the AMA House of Delegates at the annual meeting held June 20-24, 1965, in New York is excerpted from a letter sent to all California Medical Association members by Dr. Ralph C. Teall, president:

1. Affirmed that: "Physicians of America pledge themselves to continue their search and activity, in whatever social environment may develop, to secure or restore the freedom, high quality and availability of medical care which has been traditional in our country."
2. Affirmed the position that "It is each individual physician's obligation to decide for himself whether the conditions of a case for which he is about to accept responsibility permit him to provide his own highest quality of medical care."
3. Reaffirmed Section 6 of the *Principles of Medical Ethics* and the Bauer amendment.
4. Reaffirmed opposition to the inclusion of the services of the four hospital-related specialties in Part 1-A of H.R. 6675.
5. Reaffirmed opposition to the compulsory inclusion of physicians under the Social Security Program.
6. Restated offer that AMA confer with President Johnson to insure high quality care and appropriate amendment of Medicare-type legislation to achieve this end.
7. Recommended appointment of representative physicians to serve on advisory committees in all Federal health care programs.
8. Recommended that a physician be appointed to be an Assistant Secretary of the Department of Health, Education, and Welfare.

California Medical Association

CMERF—

How You Can Support It

During the past several months, California Medicine has carried a number of articles describing the activities, and reporting on the research projects being undertaken by the California Medical Education and Research Foundation.

CMERF, as physicians of California are well aware by this time, is supporting medical education efforts and is sponsoring research studies related to the social and economic problems of medical care and medical practice. Whereas support of our Foundation has previously come from private and public agencies, the board of directors has now decided that greater efforts should be expended in providing individual physicians and various community organizations with an opportunity to support its work in the future.

The California Medical Education and Research Foundation, as a nonprofit, tax exempt organization supported by the California Medical Association, is in an excellent position to support worthwhile research activities and studies, including the encouragement and development of projects in the field of continuing education.

The Scientific Board and the Bureau of Research and Planning of the CMA are just two of the qualified groups to which monies can be disbursed for meritorious activities. Several important proposals for studies in the fields of medical education and socio-economic research merely await the availability of funds.

At the conclusion of this article are some of the forms which may be used in making bequests for medical education and research in the social and economic aspects of medical care and medical practice. Physicians are invited to use whichever form represents the expression of their intentions. They are similarly invited to call this opportunity to the attention of their friends, acquaintances, and organizations which may be interested in contributing to the Foundation dedicated to the improvement of the health of the public.

The cooperation of physicians in the fund-raising endeavor of the California Medical Education and Research Foundation is most sincerely appreciated.

Ralph C. Teall, M.D., *President*
California Medical Education and
Research Foundation

Suggested Request Forms

The following are some of the forms which may be adapted in making bequests for medical education and research in the social and economic aspects of medical care and medical practice.

RALPH C. TEALL, M.D.	President
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Prospective donors would be well-advised, however, to consult with their lawyers on the exact language to be used, so that the bequest is a true and legally valid expression of their intentions.

1. To convey a cash bequest to the California Medical Education and Research Foundation (CMERF).

(For use when the object is support of research in general.)

"I give and bequeath to the California Medical Education and Research Foundation (CMERF), 693 Sutter Street, San Francisco, California, the sum of........................ dollars ($.............................) to be used for medical education and research in the social and economic aspects of medical care and medical practice."

2. To CMERF for general purposes.

(For use when CMERF will apply and allocate the funds, and when the object is support of medical education in general, and research in the social and economic aspects of medical care and medical practice.)

"I give and bequeath to the California Medical Education and Research Foundation (CMERF), 693 Sutter Street, San Francisco, California, the sum of........................ dollars ($.............................) to be used, at the discretion of its Board of Directors, for medical education and research in the social and economic aspects of medical care and medical practice."

3. To CMERF for general purposes with expression of intent.

(For use when CMERF will apply and allocate the funds, and when the object is to allow the CMERF to use its discretion in applying the funds in support of medical education and research in the social and economic aspects of medical care and medical practice, but where the donor wishes to convey his nonbinding desire as to how the funds might be used.)

"I give and bequeath to the California Medical Education and Research Foundation (CMERF), 693 Sutter Street, San Francisco, California, the sum of........................ dollars ($.............................) to be used, at the discretion of its Board of Directors, for (medical education) (research in the social and economic aspects of medical care and medical practice).

"However, this expression of my desire is not to limit the ability or right of the Board of Directors to use the money for any other research which it feels more essential."

4. To CMERF for categorical purpose.

(For use when the donor wishes CMERF to restrict the use of his funds to a certain category of research and activity.)

"I give and bequeath to the California Medical Education and Research Foundation (CMERF), 693 Sutter Street, San Francisco, California, the sum of........................ dollars ($.............................) to be used for (medical education) (research in the social and economic aspects of medical care and medical practice).

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PLAN **YOUR** CONTRIBUTION TO THE PROGRAM **TODAY**

JUNIUS B. HARRIS, M.D.

Junius B. Harris, one of Sacramento's most respected, most admired and most colorful surgeons in recent history, and a former president of the California Medical Association, died May 28 following a long cardiac illness. He was 83 years old.

June, as he was known to all, graduated from Cooper Medical College, now a part of Stanford, in 1908 and began his medical career even before graduation when he was called upon to care for victims of the San Francisco earthquake and fire of 1906.

Following an internship in Sacramento he settled in the community and in a few years established himself as not only a proficient surgeon and teacher but as a community leader, a hospital leader and an ebullient personage.

In 1915 he served as president of the Sacramento Society for Medical Improvement (now Sacramento County Medical Society) and in 1923 was one of the founders of Sutter Memorial Hospital, where he served on the staff and as a trustee. His surgical skill was demonstrated to many students who came under his tutelage over a long and glorious career.

The California Medical Association elected him president in 1931 and the American Medical Association chose him as vice-president in 1937. From 1928 to 1940 he served as chairman of the CMA Committee on Public Policy and Legislation and made that post into one of the truly important committee appointments in the CMA. He was greatly admired and respected by the members of the Legislature. At one time or another he also served on the State Board of Medical Examiners and the State Board of Health.

In the community June established himself as an authority on the history and mores of the Mother Lode days and even built a structure at his own home to house many of the relics of the gold rush. He was also active in Rotary, the Shrine, Native Sons, Chamber of Commerce and various other organizations. At one time he served as president of a savings and loan association. His place in the community was attested to in 1957, when more than 1,100 people attended a testimonial dinner for him. His contemporaries were some of the foremost medical men we have had in California.

June took an active part in various political campaigns. He served as a campaign director when Governor Hiram Johnson was elected to the U. S. Senate, managed a campaign committee when Earl Warren was elected governor of California and did the same chore when Goodwin J. Knight was elected to that post.

A lover of the outdoors, he was an expert horseman and participated in several riding groups. His personal entertaining for groups was always arranged around the outdoors and the Mother Lode days of California.

Doctor Harris was the father of four sons, two of them physicians, and two daughters. His widow also survives.

Dwight H. Murray, M.D.

In Memoriam

Burcky, Frederic William, San Marino. Died March 19, 1965, in Pasadena, aged 74, of cancer of the lung. Graduate of Rush Medical College, Chicago, Illinois, 1919. Licensed in California in 1943. Doctor Burcky was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Dickerson, Dorrell Ghio, Los Angeles. Died May 10, 1965, in La Canada, aged 72, of arteriosclerotic heart disease. Graduate of George Washington University School of Medicine, Washington, D.C., 1917. Licensed in California in 1932. Doctor Dickerson was a member of the Los Angeles County Medical Association.

◆

Dodd, John Morris, Jr., Santa Barbara. Died June 3, 1965, in Santa Barbara, aged 65. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1926. Licensed in California in 1926. Doctor Dodd was a member of the Santa Barbara County Medical Society.

◆

Edward, Joseph T., Pasadena. Died May 6, 1965, in Pasadena, aged 97. Graduate of Illinois Medical College, Chicago, 1902. Licensed in California in 1919. Doctor Edward was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Erickson, A. A. (Adolph), San Gabriel. Died May 11, 1965, in West Covina, aged 57, of hepatic failure. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1939. Licensed in California in 1939. M.D. degree from California College of Medicine, 1962. Doctor Erickson was a member of the Forty First Medical Society.

◆

Gottschalk, Adolph, San Francisco. Died May 18, 1965, in San Francisco, aged 87. Graduate of the College of Physicians and Surgeons of San Francisco, 1909. Licensed in California in 1910. Doctor Gottschalk was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

◆

Hardisty, Norris M., Palm Springs. Died April 21, 1965, aged 61. Graduate of the University of Michigan Medical School, Ann Arbor, 1929. Licensed in California in 1950. Doctor Hardisty was a member of the Riverside County Medical Association.

Harris, Junius B., *Sacramento*. Died May 28, 1965, in Sacramento, aged 83. Graduate of Cooper Medical College, San Francisco, 1908. Licensed in California in 1908. Doctor Harris was a member of the Sacramento County Medical Society.

◆

Irvin, Charles Earl, Anaheim. Died September 21, 1964, in Redlands, aged 77, of cerebral vascular accident. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1912. Licensed in California in 1936. Doctor Irvin was a member of the Orange County Medical Association.

◆

Krebs, Otto F., Woodside. Died May 31, 1965, in Woodside. Graduate of the College of Physicians and Surgeons of San Francisco, 1908. Licensed in California in 1909, Doctor Krebs was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

◆

Leisy, Melvern Krehbiel, Altadena. Died in an airplane crash, May 29, 1965, aged 42. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1950. Licensed in California in 1952. Doctor Leisy was a member of the Los Angeles County Medical Association.

◆

Levey, Philip, Beverly Hills. Died May 19, 1965, in Beverly Hills, aged 75, of coronary thrombosis. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1913. Licensed in California in 1937. Doctor Levey was a member of the Los Angeles County Medical Association.

◆

Long, Ernest Jean, Kentfield. Died May 11, 1965, in Fairfax, aged 42. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1953. Licensed in California in 1954. Doctor Long was a member of the Marin Medical Society.

◆

Lord, Dorothy Cerita, Downey. Died May 27, 1965, in Los Angeles, aged 64. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1934. Licensed in California in 1934. Doctor Lord was a member of the Los Angeles County Medical Association.

◆

MacLennan, Alexander Livingston, Pasadena. Died January 31, 1965, in Hemet, aged 87, of cardiac insufficiency. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1907. Licensed in California in 1931. Doctor MacLennan was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

McDowell, Arthur J., San Rafael. Died May 23, 1965, in San Rafael, aged 64. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1933. Licensed in California in 1933. Doctor McDowell was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

Moses, Paul Josef, San Francisco. Died June 7, 1965, in San Francisco, aged 68, of cancer. Graduate of Universitat Kohn (Cologne) Medicinische Fakultat, Koln, Prussia, Germany, 1922. Licensed in California in 1937. Doctor Moses was a member of the San Francisco Medical Society.

✣

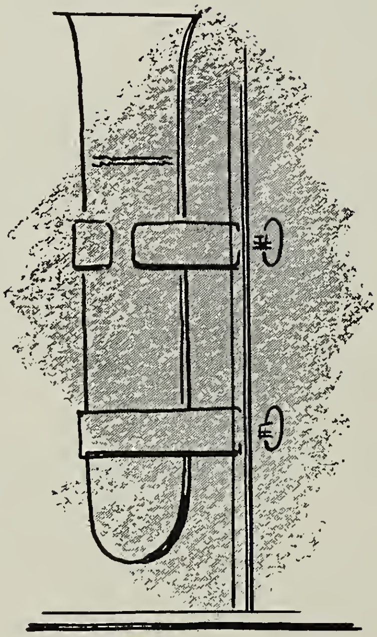
Myers, Clarence Cecil, San Diego. Died May 21, 1965, aged 68. Graduate of Ohio State University College of Medicine, Columbus, 1927. Licensed in California in 1952. Doctor Myers was an associate member of the San Diego County Medical Society.

✣

Stansfield, Joseph Thomas, San Francisco. Died May 14, 1965, aged 48, of tracheal occlusion of strangulation when trachea was occluded by swallowed food. Graduate of Louisiana State University School of Medicine, New Orleans, 1942. Licensed in California in 1942. Doctor Stansfield was a member of the San Francisco Medical Society.

✣

Topham, Edward, San Francisco. Died May 21, 1965, in San Francisco, aged 86. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1902. Licensed in California in 1902. Doctor Topham was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.



LETTERS *to the Editor*

Quality of Care

CONGRATULATIONS on the excellent symposium on virology appearing in your May issue. Many practicing physicians throughout the country will read this symposium and, as a result, many patients will benefit. Is it reasonable to observe that the symposium is one of the many intellectual products of our free enterprise system?

To maintain that system and to sustain its milieu will be indeed difficult if proposed federal legislation is passed. Indeed, the latter would place many practicing physicians in an intolerable dilemma. As members of the AMA they know that section 6 of the Principles of Medical Ethics reads: "A physician should not dispose of his services under terms or conditions which tend to interfere with or impair the free and complete exercise of his medical judgment and skill, or tend to cause a deterioration of the quality of medical care." They likewise know that the proposed legislation will do exactly that.

What shall be our policy? To look after the needy elderly (as at present) and to refuse to accept governmental payments or otherwise officially partake of the new scheme? Comments from your readers should be of interest and guidance in establishment of statewide policy.

L. H. GARLAND, M.D.

Human Pasteurellosis

Activation of Interest in Some Latent Problems

CLASSIC CONSIDERATION of human infections due to members of the genus *Pasteurella* is concerned with plague *(P. pestis)* and tularemia *(P. tularensis).* There have been extensive investigations on plague and tularemia in the U.S. and elsewhere in the world which now provide excellent clinical and epidemiologic pictures of these two diseases.

However, there are at least four other species of *Pasteurella (hemolytica multocida, pneumotropica,* and *pseudotuberculosis),* known human pathogens, for which we have little or no understanding of their clinical importance or epidemiologic patterns. Each species has been recovered from a variety of domestic and sylvatic animal reservoirs and each is, to some degree, a veterinary medical problem. Although a measure of the importance of these diseases in domestic animals in the United States is available from U.S. Department of Agriculture statistics, no comparable morbidity figures are reported for man. The occasional case reports that are published indicate, nevertheless, that a problem exists. The question remains, "how extensive is the problem?"

The first human infection due to *P. multocida* to be reported (1913) was a case of puerperal fever. Numerous cases have been reported since, involving respiratory tract infections, appendicitis, bite-wound infections, as well as other forms.[1]

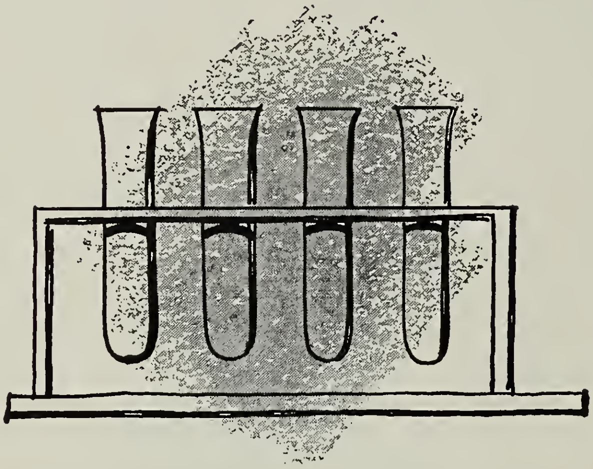
Until the 1950's, cases of *P. pseudotuberculosis* infection were considered rare, with less than 20 reports of fatal septicemia appearing in the literature. Recently, however, several hundred cases of mesenteric adenitis, often confused with acute appendicitis, have been observed primarily in Europe. In addition, recent cases of erythema nodosum as well as other forms have been described. Furthermore, *P. pseudotuberculosis* is of considerable importance as a source of diagnostic confusion due to the many cultural and biochemical characteristics that this organism shares in common with *P. pestis.*[2]

One case of *P. hemolytica* infection simulating ulceroglandular tularemia has been reported.[3] Atypical strains of *P. hemolytica* have been isolated from the respiratory tract[4] and from a case of endocarditis.[5] A number of isolations of *P. pneumotropica* have been obtained from the respiratory tract.[6]

No assessment of the importance of these agents as causes of disease in man in the United States can be made unless clinical and laboratory data can be accumulated. As a step in the right direction, it is suggested that clinical resumes, cultures, and paired sera from any patients, whether typical or atypical cases, be submitted to the U.S. Public Health Service, Communicable Disease Center, San Francisco Field Station, for further study and/or tabulation.

William T. Hubbert, D.V.M., Ph.D.
CDCA, San Francisco Field Station
15th Avenue and Lake Street, Building 18
San Francisco 94118

1. Henderson, A.: Antonie van Leeuwenhock, 29:359, 1963.
2. Mollaret, H. H.: Le Bacille de Malassez et Vignal, Caracteres Culturaux et Biochemiques, Paris, 1962, 131 pp.
3. Muraschi, T. F., Smith, C. K., and Miller, J. K.: New York State J. Med., 62:3137, 1962.
4. Hoogendijk, J. L.: Antonie van Leeuwenhock, 28: 315, 1962.
5. Doty, G. L., Loomus, G. N., and Wolf, P. L.: New Eng. J. Med., 268:830, 1963.
6. Henriksen, S. D.: Acta Path. Microbiol. Scand., 55:355, 1962.



WOMAN'S AUXILIARY

to the California Medical Association

Rx: A Program

"Doctors are so aloof; they think they walk hand in hand with God." "Modern doctors are just plain lazy—try to get one out at night!" "The AMA dictatorship is obstructing social and economic reforms." "My father's doctor was a trusted and personal friend; today, my doctor doesn't care about me." "Doctors are reactionary; they are against everything." "Doctors make too much money."

Communication is a two-way street—*transmitting* and *listening*. Never before in the history of American medicine have we heard so much complaint and criticism about physicians. There is an undercurrent of discontent about him; discontent born of the changing times—scientific, economic and political.

Unjustified accusations cry for refutation and have intensified the public relations consciousness of the profession's closest ally—The Woman's Auxiliary.

We have seen a profession, schooled and dedicated to the service of mankind, struck a mighty blow in Congress on April 8, 1965, with the passage of medicare by the House of Representatives. We are acutely aware of the consequences upon the health care of the American people.

The question arises: How have we been *transmitting?* Have we been living up to our full potential to mold public opinion, or only ambling? An inventory of county program reports from up and down the state indicates a cognizance that perhaps we, ourselves, have not done enough to dispel the many misconceptions regarding the medical profession's contributions to society.

The Woman's Auxiliary's program offers an ideal instrument for initiating constructive action to shape the critical trends of our times. We have worthy goals. However, unexpressed ideas are of no more effect than the embryo of a seed before it burgeons. We are evolving, yet if we have not grown in stature and purpose with each passing month and year, we cannot justify our existence as an organization.

One of the major purposes of the Auxiliary program is to interpret the medical profession and its stand on social issues to a misunderstanding public. This interpretation is not confined to verbal expression alone; it is also demonstrated through service and the very real concern for a way of life that denies the charge of purely material values. Our concern is rooted in a sincere concern for humanity, as is that of the medical profession.

Program within the Auxiliary is *not* a series of fashion shows, films, teas and bridge parties. We are *not* a party-giving country club set, indulging our privileges and merely hoping for peace. The Auxiliary is a *working* organization with a program that coordinates a wide variety of projects which serve to train and guide its members toward a life of constructive action in the promotion of health, peace, justice and love.

Regarding projects, to name only a few:

Legislation has been our top priority project. Busy members realize they must not only create a home for their families, but also a world in which they can live and grow in freedom. Legislation is a community service as much as the Auxiliary Homemaker Service.

Health Careers. Through the sponsoring of Future Nurse Clubs and Health Career Clubs in high schools, combined with presentations of county "Career Days," a superior effort in vocational guidance is helping young people to find their life's work. Scholarships and loans are made available to these students.

AMA-ERF. The Auxiliary is proud of its success in raising funds to sustain its own ranks, independent of government handouts. California has been a pace-setter in this field.

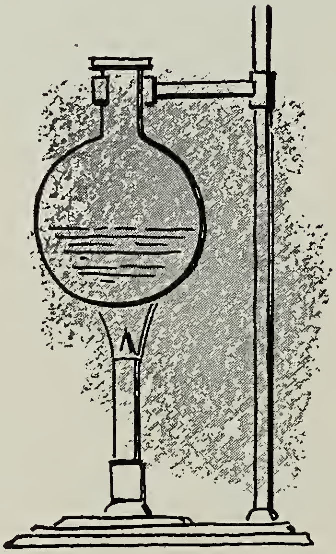
Community Service: Physicians' wives are generally outstanding community leaders, giving freely of their energies to raise funds for local hospitals, orphans homes and the like. In addition, they serve as volunteers for work at blood banks, health agencies, Red Cross and hospitals. They provide homemaker services, "Meals on Wheels" for shut-ins, training for Good Emergency Mother Substitutes. They disseminate safety information, they help expose quackery and they promote rural health.

International Health Activities. Physicians' wives are proving to be ambassadors of good will and home-front diplomats. Drugs and health supplies are collected in huge amounts and shipped to the medically indigent throughout the world through the Direct Relief Foundation in Santa Barbara. Foreign physicians and students at hospitals are being invited into our homes and entertained.

These are typical items in the Auxiliary's *program.*

Doctor, be interested in your wife's participation in Auxiliary.

Mrs. Kenneth J. McNiece
2nd Vice-President and
Program Chairman
Woman's Auxiliary to the
California Medical Association



NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

The UCLA School of Public Health has announced **two grants** from the U.S. Public Health Service for the training of students **in the field of gerontology.** Applicants with academic backgrounds in psychology, sociology, anthropology, medicine and social work may apply.

Stipends are from $250 to $400 a month depending upon level, plus dependency allowance, tuition and fees. The program has two purposes: (1) to train personnel for psychological, sociological, and epidemiological research in gerontology, and (2) to train research-oriented program personnel for community-based gerontological service programs.

Applicants should address D. M. Wilner, Assistant Dean, UCLA School of Public Health, Los Angeles 90024.

* * *

Dr. Clyde R. Goodheart has been named an associate member of the American Medical Association Education and Research Foundation's Institute for Biomedical Research.

At present, Dr. Goodheart is associate professor of pediatrics at the University of Southern California School of Medicine, and shares responsibility for the virology division at Children's Hospital of Los Angeles. His major research interests have been basic virology and cell physiology. His present research includes the study of intracellular mechanisms in an attempt to explain how viruses may cause cells to become malignant.

SAN FRANCISCO

Mr. Harold H. Hixson, Administrator of University of California Hospitals, San Francisco Medical Center, was installed as president of the Association of Western Hospitals at the annual convention April 29 in Seattle.

GENERAL

Both the **Woman's Auxiliary** to the California Medical Association and the Woman's Auxiliary to the Los Angeles County Medical Association have received awards for outstanding efforts in the American Medical Association Education and Research Foundation program in 1964-65. The presentations were made during the 42nd annual convention of the Woman's Auxiliary to the AMA, held in New York, June 20-24.

The California Auxiliary made the **greatest contribution** of any state group in the over 3,000 member category—$45,869. With a membership of 2,177, the Los Angeles Auxiliary raised $18,978. The entire national Auxiliary's contribution was $320,122, part of which will be given to medical schools for unrestricted use. The remainder will go to the student loan guarantee fund which makes possible long-term bank loans to medical students, interns and residents, with no payment due on either principal or interest until five months after completion of all training.

OBSTETRICAL ALLOWANCE FOR MILITARY MEDICARE RAISED

The Maximum Medicare allowance for complete obstetrical care for dependents of active military personnel has been increased from $150 to $175. The increase became effective July 1.

Approval of the increase followed consultations between the California Medical Association, California Physicians' Service and the U.S. Department of Defense.

Comparisons of previous maximum obstetrical allowances with those now in effect follow:

CODE	SERVICE	PREVIOUS	IN EFFECT
4821	Obstetrical delivery, including complete antepartum and postpartum care	$150	$175
4822	Obstetrical delivery, excluding antepartum and postpartum care following hospitalization	85	85
4823	Antepartum care, complete period	65	75
4824	First Trimester (first 14 weeks of pregnancy)	15	25
4825	Second Trimester (next 13 weeks of pregnancy)	15	15
4826	Third Trimester (after 27 weeks of pregnancy)	35	35
4827	Obstetrical delivery, including complete postpartum care	95	100
4828	Complete postpartum care	10	15
	Minimum fee for antepartum care	10	15

* * *

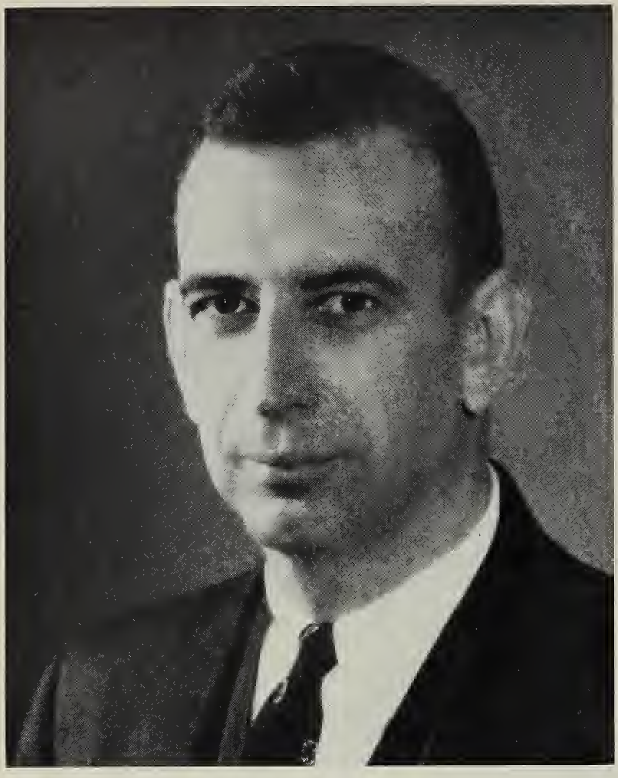
Dr. Malcolm H. Merrill, director of the California State Department of Public Health, has been appointed chairman of the regional committee for the San Francisco forum of the 1965 National Conference on Community Health Services. The conference has been called by the National Commission on Community Health Services and its sponsors, the National Health Council and the American Public Health Association.

At the San Francisco Forum, to be held September 8-11, 300 invited participants from the western region of the United States will discuss and respond to recommendations keyed to health services for the nation's communities.

New Dean at Stanford

At the beginning of this month Dr. Robert J. Glaser, formerly president of Affiliated Hospitals Center and professor of social medicine at Harvard Medical School, became dean of Stanford University School of Medicine and vice president for medical affairs.

Dr. Glaser succeeds Dr. Sidney Raffel who has been acting dean since Dr. Robert Alway resigned a year ago



DR. ROBERT J. GLASER

to return to full time teaching. Dr. Raffel will resume his duties as professor and executive head of the Department of Medical Microbiology.

At the time Dr. Glaser's appointment was announced last February, after an eight-month search for a dean by a special faculty committee, Dr. J. E. Wallace Sterling, president of the university, said:

"Dr. Glaser brings to Stanford an unusual combination of academic and administrative experience. He is nationally recognized for his concern to bring to patient care the best that medical science and teaching can provide.

"He has had experience in building a medical center, having completed one at the University of Colorado where he served as vice president for medical affairs and dean. For the past two years he has been associated with an ambitious and unique project which envisions a new kind of hospital complex in the vicinity of Harvard Medical School. The Stanford University School of Medicine is fortunate to be able to draw on Dr. Glaser's talents as scientist, teacher, and administrator."

A graduate of Harvard College in 1940 and of Harvard Medical School in 1943, Dr. Glaser interned at Barnes Hospital in St. Louis. After completing his residency training in medicine at Peter Bent Brigham Hospital in Boston and the Barnes Hospital he joined the faculty of Washington University School of Medicine in 1947.

His academic and administrative positions included assistant professor of medicine, associate dean of the faculty of medicine, and associate professor of medicine. He also acted as chief of the Division of Immunology from 1954 to 1957. In 1957 he became dean and professor of medicine at the University of Colorado School of Medicine.

Dr. Glaser returned to Harvard in 1963 to coordinate the planning of a new hospital complex which would tie in Harvard Medical School with six affiliated hospitals. Throughout his professional life, the new dean has devoted a large portion of his research activity to the rheumatic diseases. He was chief of the Rheumatic Fever Clinic in the Washington University Clinics, consultant in rheumatic fever to the State of Missouri Crippled Children's Service, and consultant in rheumatic disease to the University of Illinois. Dr. Glaser also has served as a member of the scientific advisory council of Rheumatic Fever Institute and the committee on prevention of rheumatic fever and bacterial endocarditis of the American Heart Association. He is a member of the National Health Research Facilities Advisory Council of the U. S. Public Health Service.

Dr. Glaser's publications include more than 40 papers, most of them on experimental streptococcal infections and rheumatic fever.

He holds memberships in the medical honorary society Alpha Omega Alpha, the society of Sigma Xi, the American Society for Clinical Investigation, and the Association of American Physicians. He is currently the editor of *Pharos,* the national publication of Alpha Omega Alpha.

Dr. Glaser was born in St. Louis. He is married and has three children. His wife is also a physician, specializing in pediatrics.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts
for Postgraduate Course Information

CMA:	**California Medical Association** For information regarding Postgraduate Institutes and Circuit Courses, Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. PRospect 6-9400, Ext. 68.
LLU:	**Loma Linda University** For information on courses contact: W. F. Norwood, Ph.D., Assistant Dean and Chairman, Division of Continuing Education, Loma Linda University School of Medicine, 1720 Brooklyn Ave., Los Angeles, California 90033, ANgeles 9-7241, Ext. 214.
PRES. MED. CTR.	**Presbyterian Medical Center** For information on courses contact: Arthur Selzer, M.D., chairman, Education Committee, Presbyterian Medical Center, Clay and Webster Streets, San Francisco 94115. WEst 1-8000.
UCLA:	**University of California at Los Angeles** For information on courses for physicians or ancillary personnel contact: Thomas H. Sternberg, M.D., Assistant Dean and Head, Continuing Education, U.C.L.A. Medical Center, Los Angeles, 90024, 478-9711, Ext. 2114.
UCSF:	**University of California, San Francisco** For information on courses for physicians or ancillary personnel contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, University of California Medical Center, Room 565-U, San Francisco 94122, 666-1692.
USC:	**University of Southern California** For information on courses contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, USC School of Medicine, 2025 Zonal Ave., Los Angeles 90033, CApital 5-1511, Ext. 300.
STAN:	**Stanford University** For information on courses for physicians or ancillary personnel contact: Roy Cohn, M.D., Associate Dean for Graduate Affairs, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto, DAvenport 1-1200.

*Fee to be announced. †Hours to be announced.

JULY

July 29-30—**Recent Trends in Strabismus Management and Treatment.** For physicians in Ophthalmology or EENT only. Thursday-Friday. $60. Pres. Med. Ctr.

July 31-August 11—**Eighth Annual Postgraduate Refresher Course.** USC in Honolulu and Maui. Saturday-Tuesday except Sunday. 4 hours and 45 minutes each day. $100.

AUGUST

August 15-18—**Advanced Seminars in Internal Medicine: Hypertension and Kidney Disease.** UCLA at Lake Arrowhead Conference Center. Sunday-Wednesday. 15½ hours. $105.

August 18-22—**Advanced Seminars in Urology.** UCLA at Lake Arrowhead Conference Center. Wednesday-Sunday. 18 hours. $110.

August 21-22—**Infertility.** UCLA. Saturday-Sunday. 14 hours. $60.

August 30-September 2—**American Hospital Association.** San Francisco. Monday-Thursday. Contact: Edwin L. Crosby, M.D., director, 840 North Lake Shore Drive, Chicago 11, Illinois.

SEPTEMBER

September 2-April 14—**Stockton Postgraduate Study Club.** 1 Thursday a month: 9/2, 10/14, 11/4, 12/9, 1/6, 2/10, 3/3, 4/14. 16 hours. Contact: San Joaquin County Medical Society, P.O. Box 230, Stockton.

September 9-11—**Saint John's Hospital Annual Postgraduate Assembly.** Thursday-Saturday. Contact: John C. Eagan, M.D., director, 1328 Twenty-second Street, Santa Monica.

September 13-19—**Pediatric Allergies.** UCSF. Monday-Sunday.*†

September 14-November 30—**Medical Radio Conferences.** UCSF. Tuesdays.

September 15-16—**Los Angeles Pediatric Society Annual Brennemann Memorial Lectures.** International Hotel, Los Angeles. Wednesday-Thursday. 9/15: 4:00 p.m. to 10:00 p.m., 9/16: 9:00 a.m. to 4:30 p.m.

September 16-December 9—**Medical Radio Conferences.** UCSF. Thursdays.

September 20-23—**Recent Advances in Internal Medicine.** UCSF. Monday-Thursday.*†

September 21-October 26—**Specific Syndromes Associated with Mental Retardation.** UCSF at Sonoma State Hospital, Eldridge. Tuesdays.*†

September 22-December 15—**Psychotherapeutic Medicine for Non-Psychiatrists.** UCSF. Wednesdays.*†

September 23-October 28—**Preventive Psychiatry.** UCSF at Modesto State Hospital, Modesto. Thursdays.*†

September 25-26—**Child Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.*†

September 25-26—**Manifestations and Therapy of Anxiety.** UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday.*†

September 28—**American Academy of Pediatrics, California Section III, Annual Seminar on Epilepsy.**

Town and Country Hotel, San Diego. Tuesday. 4 hours. $10. Contact: J. Richard Hill, M.D., 525 Hawthorn Street, San Diego.

September 29-30—**Los Angeles County Heart Association Annual Fall Symposium on Cardiovascular Disease.** Statler Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hours. Contact: Harold Miller, M.D., chairman, Professional Education Committee, 2405 West Eighth Street, Los Angeles 90057.

September 29-October 1—**San Francisco Heart Association Annual Postgraduate Symposium on Heart Disease.** St. Francis Hotel, San Francisco. Wednesday-Friday. 18 hours. Contact: Mrs. Frances MacKinnon, 259 Geary Street, San Francisco.

OCTOBER

October 1-2—**San Diego County Heart Association Annual Professional Symposium on Heart Disease.** Town and Country Hotel, San Diego. Friday-Saturday. 8 hours. Contact: James E. Lasry, M.D., chairman, Professional Education Committee, 3545 4th Avenue, San Diego 92103.

October 1-2—**Urology.** UCSF. Friday-Saturday.*†

October 5-November 30—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesdays.*†

October 7-9—**Obstetrics and Gynecology.** UCSF. Thursday-Saturday.*†

October 8-9—**Western Industrial Medical Association.** Hilton Hotel, San Francisco. Friday-Saturday. Contact: Christine Einert, M.D., 629 Euclid Avenue, Berkeley 94708.

October 9—**Immunological Disease and Infectious Disease in Children.** Children's Hospital Medical Center, 51st and Grove Streets, Oakland. Saturday. 7 hours. Contact: Children's Hospital Medical Center.

October 9-10—**Cytology for Pathologists.** UCSF. Saturday-Sunday.*†

October 12—**Northeastern California Rheumatoid Foundation Seminar: Medical and Surgical Aspects of Arthritis.** Mercy Hospital, Sacramento, Tuesday. Contact: Harold B. Strauch, M.D., 4101 J Street, Sacramento.

October 12-November 16—**Neuropsychiatry in Daily Practice.** UCSF at Agnews State Hospital, San Jose. Tuesdays.*†

October 15-16—**Central Nervous System Infections.** UCSF. Friday-Saturday.*†

October 15-16—**Logical Glaucoma Therapy.** UCSF. Friday-Saturday.*†

October 16—**Imperial County Medical Society Program on Emergency Room Treatment.** Barbara Worth County Club. Saturday. 8 hours. Contact: Imperial County Medical Society, El Centro.

October 20-April 20—**Basic Science Course in Ophthalmology.** UCLA. Wednesdays. Lecture: 49 hours, Lab: 31½ hours. $175 for full course.

October 22-24—**California Society of Internal Medicine Annual Meeting.** Hotel Del Coronado, Coronado. Friday-Sunday. Contact: Nancy V. Louw, executive secretary, California Society of Internal Medicine, 350 Post Street, San Francisco 94108.

October 23—**Endocrine and Metabolic Disorders.** UCSF at Childrens Hospital, San Francisco. Saturday.*†

October 23-24—**Practical Management of Surgical Problems.** UCSF at Franklin Hospital, San Francisco. Saturday-Sunday.*†

October 24-27—**California Academy of General Practice Annual Scientific Assembly.** Statler Hotel, Los Angeles. Sunday-Wednesday. 13 hours. Contact: Mr. William W. Rogers, executive secretary, California Academy of General Practice, 9 First Street, Room 900, San Francisco.

October 27-29—**American Thoracic Society Postgraduate Course on the Evaluation of Pulmonary Function.** Stanford University School of Medicine, Palo Alto. Wednesday-Friday. 80 hours. Contact: Rudy Glover, Tuberculosis and Health Association of California, 424 Pendleton Way, Oakland.

October 29—**Kern County General Hospital Postgraduate Conference.** Kern County General Hospital, 1830 Flower Street, Bakersfield. Friday. 8 hours. Contact: George A. Paulsen, M.D., chairman, Postgraduate Conference Committee, Kern County General Hospital.

October 29-30—**Arthritis in Practice.** UCSF. Friday-Saturday.*†

NOVEMBER

November 5-6—**California Hospital Seminar on the Acute Abdomen.** California Hospital, 1414 South Hope Street, Los Angeles. Friday-Saturday. 12 hours. Contact: Kenneth L. Senter, M.D., Director of Medical Education, California Hospital.

November 5-6—**Diseases of the Biliary System.** UCSF. Friday-Saturday.*†

November 6-7—**Postgraduate Seminars in Psychiatry.** UCSF at Fresno Community Hospital, Fresno. Saturday-Sunday.*†

November 10—**The Southern California Annual Science Lecture of The American College of Physicians.** Statler Hilton Hotel, Los Angeles. Wednesday, 6:30 p.m. Contact: W. Philip Corr, M.D., Governor for Southern California, The American College of Physicians, 3660 Arlington Avenue, Riverside 92506.

November 11-13—**Gerontological Society.** Ambassador Hotel, Los Angeles. Thursday-Saturday. Contact: Mrs. Marjorie Adler, MA, Gerontological Society, 661 S. Euclid, St. Louis 63110.

November 11-13—**Annual Western Institute on Epilepsy.** Kona Kai Club, Shelter Island, San Diego. Thursday-Saturday. $10. Contact: Manuel Barba, M.D., San Diego County Epilepsy Society, 1612 30th Street, San Diego 92102.

November 12-13—**Kaiser Foundation Hospitals Symposium on Genetics.** Statler Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Herman Weiner, M.D., Permanente Medical Group, 1505 North Edgemont, Los Angeles 90027.

November 13-14—**First Annual Clinical Cancer Conference.** UCSF. Friday-Saturday.*†

November 17—**Santa Barbara Cottage and General Hospitals Program on Advances in Medical Practice.** Santa Barbara Cottage Hospital. Wednesday. 3

hours. Contact: C. A. Domz, M.D., 317 West Pueblo, Santa Barbara.

November 19-20—**Musculoskeletal System: Congenital and Heritable Defects.** UCSF. Friday-Saturday.*†

DECEMBER

December 1-4—**Ophthalmology Symposium: Retinopathy and Diabetes.** UCSF. Wednesday-Saturday.*†

December 3-4—**Vectorcardiography.** UCSF. Friday-Saturday.*†

December 11—**Medical Emergencies.** Pres. Med. Ctr. Saturday.*†

December 11-12—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton. Saturday-Sunday.*†

JANUARY

January 19—**Riverside County General Hospital Postgraduate Assembly.** Riverside County General Hospital. Wednesday. 12 hours. Contact: Harold A. Roth, M.D., Riverside County General Hospital, 9851 Magnolia Avenue, Riverside 92503.

January 20-21—**New and Old Antibiotics.** USC. Thursday-Friday.*†

January 28—**Nuclear Medicine.** USC. Friday.*†

January 28-30—**Clinical Conference in Pediatric Anesthesiology.** Friday-Sunday. Contact: M. Digby Leigh, M.D., Childrens Hospital of Los Angeles, 4614 Sunset Blvd., Los Angeles 90027.

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The Physician's BOOKSHELF

PROGRESS IN CLINICAL CANCER—Volume I—Edited by Irving M. Ariel, M.D., F.A.C.S., Associate Clinical Professor of Surgery and Attending Surgeon, New York Medical College, Flower and Fifth Avenue Hospitals; Attending Surgeon and Chief of the Soft Somatic Tissue Tumor Service, Hospital for Joint Diseases; Attending Surgeon, Pack Medical Group, New York, N.Y. Grune & Stratton, Inc., New York and London, 1965. 789 pages, $35.00.

This ample monograph consists of 14 sections, contributed by 72 authors; it is essentially a "Yearbook of Cancer."

After some introductions, there is a short section dealing with general considerations of cancer, followed by sections dealing with the surgical, radiological and chemotherapeutical treatment of this disease. There are then sections dealing with cancer of specific sites such as head and neck, breast, lung, and gastrointestinal tract. Finally, sections dealing with lymphoma, tumors of muscle, and "specific tumors of other sites."

In the introduction, the editor quotes Wangensteen to the effect that "all that is new is not necessarily good." It is the expressed goal of the editor to present those things which are not only new but which have also proved to be good. Alas, this reviewer notes only one paper in the entire monograph in which controls were used in a clinical therapeutic study. It is therefore to be hoped that the anticipated subsequent annual volumes will stress the need for such and perhaps reprint the excellent control studies now emanating from such cancer centers as the Christie Hospital in Manchester.

In an interesting chapter by Pack entitled "Perspective and Prospective View," the great usefulness of low-voltage, short-distance radiotherapy (60 KV) is properly stressed "This miniature instrument . . . is as useful today as it was 30 years ago for selected therapy of certain cancers of the skin and lip." To these we would add, eyelid and superficial layers of the globe.

The control study above referred to was one dealing with 666 female patients with carcinoma of the breast, one-half treated by extended radical mastectomy and one-half by simple mastectomy followed by radical postoperative radiotherapy. The patients in the two groups were approximately equally distributed by stage of disease and by age. The five year results are available for all cases, and the ten year results for almost 200 of them. The five year survival rate in the radically treated group is 56 per cent, and in the group treated by simple mastectomy and postoperative radiotherapy 55 per cent. The respective ten year survivals are 35 per cent and 34 per cent. This excellent control study should be read by all interested in the problem of cancer treatment; its reproduction alone warrants the wide use of this monograph. (Kane, S. & Johansen, H. "Mammary Carcinoma.")

In the section on possible radiation-induced carcinoma, Pifer & Hempelmann conclude that "none of the prospective investigations have been properly controlled, and for this reason the treated children studied may represent a selected group predisposed to develop thyroid neoplasia without exposure to ionizing radiation."

In a chapter dealing with the natural history of bronchial cancer it is observed that like most human cancer, this disease is usually of many *years,* rather than *months* duration prior to diagnosis. Therefore, the use of the term "early" in its ordinary recognition is neither scientific nor valid. Indeed, the more one considers the problem of human cancer the more it is evident that we usually are consulted during the last scene of a four act drama; the real solution to the problem must be one of prevention rather than diagnosis or treatment. Until such solution is at hand we must of course continue efforts to diagnose it while still localized, and treat it by suitable radical measures in an attempt to cure. Steadily rising cancer incidence and mortality rates (that accompany our increasing longevity) call for skeptical analysis of most of the ostensibly new, but still uncontrolled therapeutic measures discussed in this well-illustrated and well-indexed work.

L. HENRY GARLAND, M.D.

* * *

STEREOSCOPIC MANUAL OF THE OCULAR FUNDUS IN LOCAL AND SYSTEMIC DISEASE—Frederick C. Blodi, M.D., Associate Professor of Ophthalmology, and Lee Allen, Associate in Ophthalmology, State University of Iowa College of Medicine, Iowa City, Iowa. With a Foreword by Alson E. Braley, M.D., Head and Professor, Department of Ophthalmology, State University of Iowa College of Medicine, Iowa City, Iowa. (Included with book are 105 stereoscopic views in full color on 15 View-Master® reels, and a View-Master® compact viewer.) The C. V. Mosby Company, Saint Louis, 1964. 132 pages, $32.50.

This is a beautifully prepared teaching manual for students, and a refresher course for experienced ophthalmologists. The stereo photographs cover a wide variety of fundus conditions, including those related to systemic diseases.

The manual comes complete with 15 stereo "reels" which may be viewed in the well known View-Masters. The manual comes complete with its own small ingenious folding View-Master which the reader may use in quiet repose under any usual lighting conditions. The reels may be used as teaching material for larger groups when projected through a stereo projector and viewed through polaroid lenses.

A foreword by Alson E. Braley traces the history and source of patient material of these excellent photographs.

There are approximately 100 accompanying photomicrographs of the histologic material relating to the stereoscopically viewed fundus photographs.

The material is an outgrowth of the popular medical exhibits by the co-authors and is a most welcome advance in teaching the clinical and laboratory aspects of fundus pathology.

There is an introductory chapter detailing the photographic techniques which encourages others to gather similar material. This manual is a "must" in the training of all ophthalmologists.

ARTHUR JAMPOLSKY, M.D.

HISTORY OF SURGICAL ANESTHESIA—Thomas E. Keys, A.B., M.A., Librarian of the Mayo Clinic, Rochester, Minnesota; Associate Professor of History and Medicine, Mayo Foundation, Graduate School University of Minnesota; Honorary Member American Society of Anesthesiologists. Dover Publications, Inc., New York, N.Y., 1963. 193 pages, $2.00 (Paperback).

This wonderful, small book is the result of revision, growth, and expansion of a chronology of anesthesia first published in 1942.

This book contains four sections; Section I entitled "The Development of Anesthesia" is the main text and is subdivided under sixteen headings. Therein is a chronological discussion of the events and people concerned with the development of anesthesia, from the early aspects of practical administration to more recent ideas in the emergence of anesthesia as a specialty. This section maintains a quite strict factual tone with minimum excursions into personality or characterization.

Sections II, III and IV occupy one half of the book and include the chronological table of events, a reference section arranged by subject and a selected reference section arranged by the author (alphabetically). Sections I and II are also provided with individual reference lists; it is thus apparent that this small volume is a treasure house of historical references.

Perhaps, part of the function of a historian is to suggest correlations between people, places and events; a mild criticism of this volume is that the author remains too factual, although this factual position is more secure than being overly imaginative.

This reviewer hopes that Professor Keys will continue to revise and amplify this volume; at present we appreciate this excellent volume.

R. W. M. BETHUNE, M.D.

* * *

HISTOPHYSIOLOGY OF SYNAPSES AND NEUROSECRETION—Eduardo D. P. de Robertis, M.D., Professor of Histology and Director Institute of General Anatomy and Embryology, Faculty of Medical Sciences, University of Buenos Aires, Argentina. A Pergamon Press Book, distributed by The Macmillan Company, New York, 1964. 244 pages, $10.00.

In a splendid volume of 244 pages, the author presents the current state of our knowledge of the snyapses and neurosecretion in the light of the recent ultra structure contributions of the electron microscope. In a most lucid but comprehensive fashion, the facts as they have recently evolved are put into perspective with previous concepts and data collected by workers during the last century.

The work is logically divided into two parts. The section on the synapse constitutes approximately three fifths of the volume and is organized into eight chapters dealing with general concepts, morphology, general ultrastructure, ultrastructure of special synapses, the localization of synaptic vesicles, certain physiological correlations, changes during degeneration and neurochemical studies.

The section on neurosecretion is organized into four chapters dealing with the hypothalamic-neurohypophyseal system, the adrenal medulla, the pineal gland, and adrenergic nerves and endings. The format presents the important historical background followed by a clear exposition, completely documented, of the present state of our knowledge of the morphology, physiology, and pathology of the synapse and anatomical substrate of neurosecretion. The electron microscopic studies take us to the macromolecular level of structure where morphology and function become very closely identified one with the other. In this area, the author has contributed fundamentally. He has described the synaptic vesicles, the sub-synaptic web, the intersynaptic filaments, etc. The rich diet of the book does not lend itself to appropriate summary in this review, but in the interest of rapid survey, each of the twelve chapters is succinctly summarized by the author.

The illustrations are clear and well reproduced. The tables are meaningful. The references are appropriately named and dated in the text and repeated without title in the reference list at the end of the book, and an index of mixed subject and author completes the volume. There are few comments that can be made which are anything but of a laudatory nature. The misspellings are few. The work should find its place upon the desk of all neurophysiologists, neuro-anatomists and electron microscopists as well as others interested in the understanding of neurotransmission. It will also be of interest to investigative endocrinologists and to all in the academic field of the neurological sciences. It will have limited appeal to the practicing clinician, but for the individual who wishes to have a comprehensive statement of our present knowledge of this most important aspect of neural function, the volume is without peer and can be highly recommended.

W. EUGENE STERN, M.D.

* * *

INDUSTRIAL AND TRAUMATIC OPHTHALMOLOGY —Symposium of the New Orleans Academy of Ophthalmology—Arthur H. Keeney, M.D., Hedwig S. Kuhn, M.D., Roderick Macdonald, Jr., M.D., Frank W. Newell, M.D., Joseph F. Novak, M.D., Ralph W. Ryan, M.D., and Lorenz E. Zimmerman M.D. The C. V. Mosby Company, St. Louis, 1964. 321 pages, $14.50.

This symposium on Industrial and Traumatic Ophthalmology brings together a distinguished panel of Ophthalmologists in a discussion of problems which are often neglected in the average residency training program.

Such chapters as "Professional Participation Inside Industry," by Hedwig S. Kuhn, M.D.; "Are the Eyes Right for the Job?" by Joseph F. Novak, M.D.; "Making the Job Easier and Safer to See" by Joseph F. Novak, M.D.; "In-plant Emergency Eye Care" by Hedwig S. Kuhn, M.D.; "How Disabled Is the Injured Eye?" by Joseph F. Novak, M.D., are particularly informative. With an increased use of nuclear materials, lasers, etc., the chapter by Dr. Frank W. Newell on "Radiant Energy and the Eye" is a must since almost any ophthalmologist can be confronted by possible radiant energy injuries. Ignorance of the problem can frequently cause unnecessary litigation.

The book is excellently bound with numerous illustrations and figures by C. V. Mosby.

ROBERT M. SINSKEY, M.D.

* * *

RESPONSE OF THE NERVOUS SYSTEM TO IONIZING RADIATION—Second International Symposium Held at the University of California, Los Angeles. Edited by Thomas J. Haley, Laboratory of Nuclear Medicine and Radiation Biology, University of California, Los Angeles, Calif., and Ray S. Snider, School of Medicine and Dentistry, University of Rochester, Rochester, N.Y. Little, Brown and Company, Boston, 1964. 749 pages, $18.50.

This collection of 40 research papers was presented at a Symposium on the Response of the Nervous System to Ionizing Radiation held at the University of California, Los Angeles, in 1963. Many of the authors are prominent in this field. The subject matter includes cytologic, biochemical, bioelectrical, functional and behavioral effects of radiation on the central and peripheral nervous systems. The studies described in these papers are largely basic in nature; there is little clinical material. This volume would prove an excellent reference work for all those interested in current research on the effects of ionizing radiation on the nervous system.

SMOKING AND YOUR LIFE—Alton Ochsner, M.D., Julian Messner, Inc., New York, 1964. 144 pages, $3.00.

This monograph consists of 10 chapters which summarize sundry observations or opinions on the effects of smoking on the heart, the respiratory system, the digestion, sex and the brain. The latter section commences as follows:

"Heavy smokers are avid television watchers. Nonsmokers would prefer to read a book. People repeatedly unemployed smoke more than people who are steadily employed. And those in jobs requiring higher education are less likely to be smokers than unskilled laborers."

Nowhere is it pointed out that while there *is* a statistical association between excessive cigarette smoking and lung cancer, such association (as was stressed in the Report to the Surgeon General) does not establish proof of causation. Many students of the problem believe that the latter requires *medical* evidence. After almost 15 years of intensive and expensive inquiry no further evidence—clinical, experimental or pathological—has been produced and the presumption of some is that there is no such evidence. The chemical in tobacco smoke allegedly responsible for human cancer has never been isolated. Lees (himself a nonsmoker) points out in the Lancet for June 20, 1964, page 1393, that lung cancer death rates in Great Britain at all ages under 55 have been declining over the past five years, despite the fact that the general population has unfortunately continued to smoke more and more. It certainly seems unlikely that one single extrinsic factor should be the sole cause of one form of cancer in a given exposed body system. Multiple factors, genetic, sex-linked and perhaps viral may well be concerned with the initiation and promotion of cancer and atherosclerosis.

Dr. Ochsner quotes portions of the work of Yerushalmy who studied the birth weight of infants born of patients who smoked, but unfortunately omits the pertinent portion which disclosed that while the children of smoking parents weighed less than those of nonsmoking parents, their perinatal mortality rate was actually lower than that of the "control" group.

This lucubration might be more cogent were the author to abjure excess of any type—eating, drinking and driving as well as smoking. Incidentally, this monograph first appeared in 1954 under the title "Smoking and Cancer"; then in 1959 it was called "Smoking and Health"; now it is "Smoking and Your Life." May we hope that the next edition (in 1970?) will be entitled "Smoking and Common Sense."

L. Henry Garland, M.D.

* * *

PRACTICAL PROCEDURES IN DIAGNOSTIC RADIOLOGY—H. M. Saxton, M.B., M.R.C.P., F.F.R., D.M.R.D., Consultant Radiologist, Guy's Hospital, London; and Basil Strickland, M.B., M.R.C.P., D.C.H., F.F.R., D.M.R.D., Consultant Radiologist, Westminster Hospital, London, and Consultant Radiologist, Brompton Hospital, London. Grune & Stratton, New York, 1964. 275 pages, $8.75.

A very practical, small book has been written by the above-named authors which should find a very useful position in the library of any radiologic department.

It goes into considerable detail, primarily in the more complicated procedures exclusive of neuroradiology, but also in the less common procedures which one tends to forget from one examination to the next. This provides, therefore, not only a particularized description of well done radiologic procedure as performed in their institution but also a ready reference book.

Its only drawback is the use of British terminology for hospital equipment, drugs, etc., that offers temporary confusion. However, the book is well conceived, well written and well worthwhile.

R. L. Scanlan, M.D.

POST-LUMBAR PUNCTURE HEADACHES—Wallace W. Tourtellotte, M.D., Ph.D., Associate Professor of Neurology, and Armin F. Haerer, M.D., Teaching Associate of Neurology, University of Michigan Medical School, Ann Arbor, Michigan; Grant L. Heller, M.D., Department of Neurology, Mount Sinai Hospital, Cleveland, Ohio; and John E. Somers, M.D., Clinical Associate in Medical Neurology, National Institutes of Neurological Diseases and Blindness, Bethesda, Maryland. With a Foreword by Russell N. DeJong, M.D., Department of Neurology, University of Michigan. Charles C Thomas, Publisher, Springfield, Illinois, 1964. 120 pages, $5.50.

This small monograph first presents a comprehensive review of the literature with an excellent bibliography and concludes that the mechanism of post-lumbar puncture headache is the escape of cerebrospinal fluid through the needle hole in the dura. Second, it analyzes their own considerable experience with lumbar punctures in normal people, as well as in different diseases. They gave consideration to factors, such as age, sex, number of lumbar punctures, length of rest, whether resting prone or supine, experience of operator (student, resident or staff) and effects of drugs. It is of interest that the incidence of headaches, when the operator is a third-year resident, is 50 per cent, while it is only 27 per cent with a student or a staff member.

Having discussed the controversies regarding the cause and treatment, they concluded that at the present time the best way to prevent and treat the post-lumbar headache is by using a small-bore needle, avoiding multiple punctures, and perhaps by maintaining a strict recumbent regimen for 24 hours without cough and strain.

The value of this monograph lies in its comprehensive review of the literature and the model of their own investigation of post-lumbar puncture headache. This will be of particular interest to persons interested in the research of headache mechanisms. However, any physician who is responsible for a lumbar puncture cannot fail but be interested, though such a physician can rapidly abstract from this monograph the facts of value to him, by reading the well-prepared short summaries at the end of each of its chapters.

Donald Macrae, M.D.

* * *

YEAR BOOK OF ANESTHESIA (1964-1965 YEAR BOOK SERIES)—Edited by Stuart C. Cullen, M.D., Professor and Chairman, Department of Anesthesia, University of California Medical Center, San Francisco. Year Book Medical Publishers, Inc., Chicago, 1964. 444 pages, $8.50.

The Year Book series has provided one of the best solutions to the problem of most doctors in learning about advances of medicine being reported in many publications. The second Year Book of Anesthesia serves this purpose for anesthesiologists, and others interested in similar problems, by providing concise informative abstracts of the essentials from 316 articles originally published mostly in late 1963 and early 1964. Abstracts are indexed both by author and subject.

Subject matter includes not only technical, pharmacologic and physiologic information related to anesthesia but also information about special patient care such as shock, transfusion, cardiac arrest, hyperbaric oxygenation, renal function, etc. Tables and figures have been reproduced to present data in some abstracts. Many abstracts are followed by pertinent observations and evaluations by the author who has a world wide reputation in teaching, research and publication.

This book was published in November 1964. It should be useful for general informative reading by those interested in basic sciences as well as those interested in anesthesiology.

John W. Pender, M.D.

AMA Biomedical Research Institute Advisors Named

Two eminent scientists were named to the Committee of Scientific Advisors of the American Medical Association Education and Research Foundation's Institute for Biomedical Research.

They are Hudson Hoagland, Ph.D., co-founder and executive director of the Worcester Foundation for Experimental Biology, and Severo Ochoa, M.D., who shared the 1959 Nobel Prize for medicine and physiology.

At the same time he announced the appointments, Raymond M. McKeown, M.D., president of the AMA-ERF Board of Directors, also announced the resignation, for reasons of health, of D. D. Van Slyke, Ph.D.

Dr. Van Slyke, member-emeritus of the Rockefeller Institute and the first recipient of an award named for him and given annually by the Association of Clinical Chemists, will, however, continue to serve the Institute as a consultant.

Dr. Hoagland, a physiologist, currently holds an appointment as Affiliated Professor of Biological Psychiatry at Boston University.

He previously taught at Harvard and Cambridge universities, and was head of the Biology Department at Clark University until 1944. In that year he and his colleague, Dr. Gregory Pincus, together started the independent Worcester Foundation for Experimental Biology.

Dr. Hoagland has published numerous works on studies dealing with neurophysiology, adrenal physiology and biochemical aspects of mental disorders, and has served on the editorial boards of three professional journals.

He has also been president of the American Academy of Arts and Sciences. Currently he serves on various visiting committees, and is a trustee of the Worcester Memorial Hospital and the Woods Hole Oceanographic Institution.

He received his Ph.D. from Harvard University in 1927, and has honorary doctorates from Colby College, Wesleyan University, Clark University and Bates College.

Dr. Hoagland received the 1965 Modern Medicine Award for Distinguished Achievement, and was named "Humanist of the year" for 1965 by the American Humanist Association.

Dr. Ochoa, a native of Spain and naturalized U.S. citizen, received his M.D. from the University of Madrid in 1929, where he lectured and headed the Medical Research Institute until 1936.

Later he conducted research in England before becoming an instructor and research associate at Washington University, St. Louis, in 1941.

He joined the staff at New York University School of Medicine the following year, and currently is Professor and Chairman of the Department of Biochemistry.

Dr. Ochoa shared the 1959 Nobel Prize with Dr. Arthur Kornberg for "their discoveries of the mechanism of the biologic synthesis of ribonucleic and deoxyribonucleic acids."

He holds honorary degrees from Washington, Glasgow, Oxford, Brazil and Wesleyan Universities and has served as president of the American Society of Biological Chemists and the Harvey Society.

Among the awards he has received are the Neuberg Medal, the Price Award of the French Society of Biological Chemistry and the Borden Award of the American Association of Medical Colleges.

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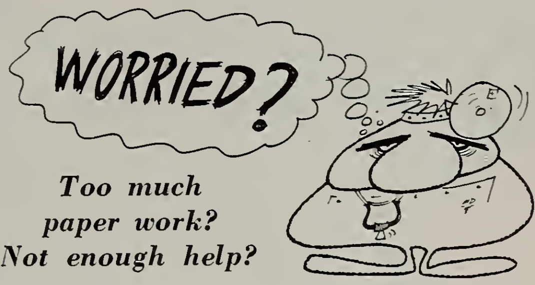

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For Children over 6 years of age—50 to 100 mg. daily in divided doses, then adjust to individual patient requirements.

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25 mg. and 50 mg. per cc.

Contraindications: Hydroxyzine pamoate is contraindicated for patients who have shown a previous hypersensitivity to it. Hydroxyzine parenteral solution is intended only for intramuscular or intravenous administration and should not, under any circumstances, be injected subcutaneously or intra-arterially.
Precautions: Hydroxyzine may potentiate the action of central nervous system depressants, narcotics such as meperidine, and barbiturates. In conjunctive use, dosage for these drugs should be decreased. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. On intravenous injection a few instances of digital gangrene have occurred distal to the injection site considered to be due to inadvertent intra-arterial injection or periarterial extravasation. Therefore, particular caution should be observed when hydroxyzine parenteral solution is administered intravenously to insure injection only into intact veins; avoid either intra-arterial injection or extravasation. Intravenous administration should be accomplished slowly, no faster than 25 mg. per minute, and not to exceed 100 mg. in any single dose.
Adverse Reactions: Drowsiness may occur which is usually transitory, disappearing spontaneously in a few days with continued therapy or correctable by dosage reduction. Dryness of the mouth may be seen with higher doses. Involuntary motor activity has been reported in some hospitalized patients on higher than recommended dosage.

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BOOKS RECEIVED

(Continued from Page 33)

and Ann Gayler Kuttner, B.S., Ph.D., M.D., Associate Professor of Pediatrics, Emeritus, New York University, Bellevue Medical Center; Visiting Scientist, Streptococcal Disease Laboratory, Sinai Hospital of Baltimore. With a special chapter on Community Health Services by Leon Gordis, A.B., M.D., Field Officer, Heart Disease Control Program, U.S. Public Health Service; Fellow in Pediatrics, Sinai Hospital and The Johns Hopkins Hospital. This is Volume II in the Series. Major Problems in Clinical Pediatrics—Alexander J. Schaffer, Consulting Editor. W. B. Saunders Company, Philadelphia and London, 1965. 242 pages, $7.50.

SHORT-TERM PSYCHOTHERAPY—Lewis R. Wolberg, M.D., with nine contributors. Grune & Stratton, Inc., New York, 1965. 348 pages, $9.75.

STUDIES IN THE PATHOLOGY OF RADIATION DISEASE—N. A. Krayevskii. Translated by A. Lieberman. English Translation Edited by Hermann Lisco and Malcolm Walker. A Pergamon Press Book, distributed by The Macmillan Company, New York, 1965. 219 pages, $15.00.

SURGERY OF THE BILIARY PASSAGES AND THE PANCREAS—Walter Hess, Privatdozent Dr. med., Zurich; Dozent of Surgery, Faculty of Medicine, University of Basle, Switzerland; formerly Professor of Surgery, Medical School, University of Alexandria, Egypt. Translated from the German by Heinrich Lamm, Dr. med., F.A.C.S., Harlingen, Texas. Operative Drawings by Ingrid Schaumburg. D. Van Nostrand Company, Inc., Princeton, New Jersey, 1965. 638 pages, $25.00.

Tracy's THE DOCTOR AS A WITNESS—Second Edition—William J. Curran, LL.M., S.M. Hyg., Edward R. Utley Professor of Legal Medicine and Director, Law-Medicine Institute, Boston University. W. B. Saunders Company, Philadelphia, 1965. 196 pages, $5.75.

Medicine, Education Commend Health Education Projects

Two television and movie organizations and one foundation have been commended for their work in health education by the Joint Committee on Health Problems in Education of the National Education Association and the American Medical Association.

Walt Disney Studios were commended "for their keen insight in considering the significance of developing health education films for the junior high schools of the United States." The Joint Committee offered its cooperation and support to this project.

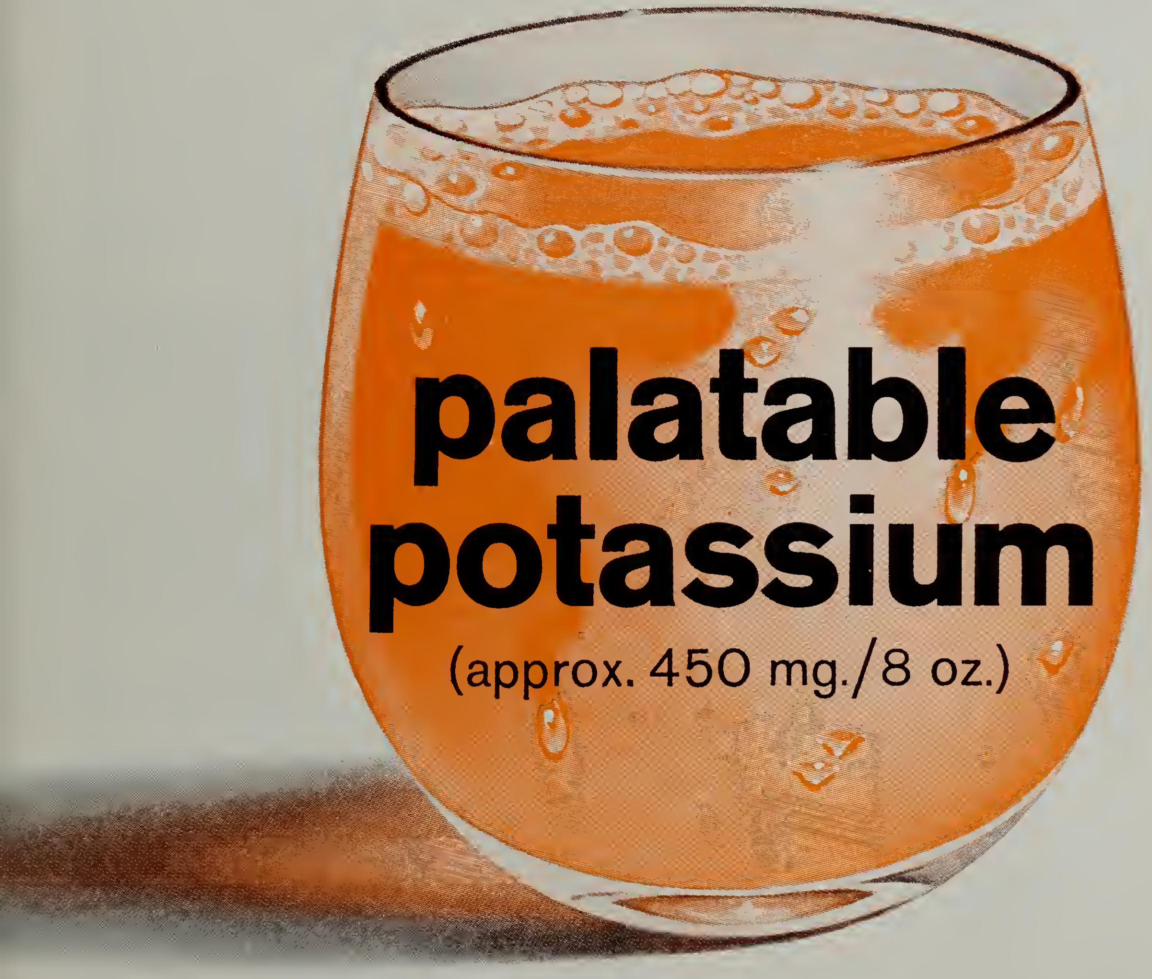
The Samuel Bronfman Foundation was commended for sponsoring National School Health Education Study, and was encouraged to continue support for research in health education.

The National Broadcasting Company was commended for its production of the program, "Mr. Novak," and was encouraged to continue the series. The Committee also urged that additional programs be concerned with health problems, such as venereal disease, unwed parents and the use of harmful substances.

Referring to "Mr. Novak," the Joint Committee said it recognizes the value such programs have for health and education.

The commendations were made at a meeting this spring of the Joint Committee on Health Problems in Education. The Committee has been a cooperative effort of education and medicine for the past 54 years.

(during diuretic therapy)



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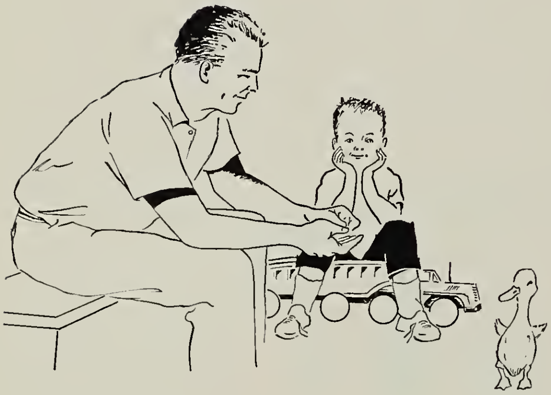
rap•port (ră•pōrt′; rá•pôr′), n. An intimate or harmonious relation.



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Should Ear Canals Be Sterilized?

Two Columbus, Ohio, surgeons say they have stopped sterilizing "normal," disease-free ear canals before otologic surgery because such canals contain no pathogenic bacteria.

Their report appears in the June *Archives of Otolaryngology,* published by the American Medical Association. The Archives' table of contents describes it as a "somewhat startling report."

"There is evidence, both bacteriological and clinical, to show that the emphasis placed by some on sterilization of the ear canal is out of proportion to its usefulness," said William H. Saunders, M.D., and John W. Ray, M.D., of University Hospital, Columbus.

In the same issue of the Archives, however, two Texas physicians state a case for ear canal sterilization.

William K. Wright, M.D. of Houston, and Paul J. Marmesh, M.D., of San Antonio, describe anti-infection measures in ear surgery and comparative tests of antiseptics.

In their study of 217 normal ear canals before stapes surgery, Drs. Wright and Marmesh found that "multiple surgical preparations, while they might not always totally sterilize the ear canal skin, will reduce the bacterial count to a point where infection is less likely to occur."

Drs. Saunders and Ray said medication "may do more harm than good" in some types of ear surgery if it reaches the middle ear. Such medication also may lull the surgeon into a false sense of security concerning the sterility of his operating field, they said.

"Five years ago," said Drs. Saunders and Ray, "after finding that the normal ear canal contains no pathogens, we decided to stop trying, by preoperative preparation, to eliminate organisms never present in the first place.

"Instead, we tightened our surgical masks and improved sterile techniques generally in the operating room. Now we never wash or instill medication of any sort into the ear canal of a patient undergoing stapedectomy (removal of the 'stirrup' ear bone), tympanoplasty (repair of the middle ear) or mastoidectomy (removal of mastoid cells or mastoid part of the temporal bone)."

Their findings that clinically normal ear canals harbor no pathogens "is at some variance" with other reports, said Drs. Saunders and Ray. They said, however, that their recent study of microflora of normal ear canals confirms earlier, similar findings by Dr. Saunders and others.

Drs. Saunders and Ray stated they were not proposing abandonment of preoperative preparation of the skin, but that "some of the painstaking systems of skin preparation devised for the ear canal are not a substitute for careful preoperative inspection the day before surgery or for rigid adherence to long-accepted surgical techniques."

AMA Book on New Drugs Designed For Physician

A book that gives physicians much needed information about new drugs is ready for distribution.

Issued by the Council on Drugs of the American Medical Association and titled simply "New Drugs," it is designed to meet the specific needs of the practicing physician for a source of up-to-date, authoritative, and unbiased information on single entity drugs introduced within the past 10 years. Physicians may buy the 500-page book from the AMA at a cost of $5.00 per copy.

Before prescribing a drug, the physician wants to know: What does it do? How effective is it in comparison with similar drugs? What are its side effects?

In medical school the physician will have learned much that he needs to know about drugs in use at that time. But a bewildering array of new drugs and new groups of drugs have come on the market in the past decade. Although new products are accompanied by advertising and prescribing information from drug manufacturers, the physician usually feels a need for an impartial evaluation of the products by other physicians—especially by physicians capable of giving expert opinions.

This is the need filled by "New Drugs."

In some ways, "New Drugs" parallels a volume formerly issued annually by the Council on Drugs under the name "New and Nonofficial Drugs." In the case of both the older book and "New Drugs," statements made about drugs are based on evaluation of laboratory and clinical evidence by the Council and its many consultant experts. Evidence is gathered from manufacturers and published scientific reports; no original laboratory or clinical research is done by the Council. Statements about a drug may be either favorable or unfavorable but inclusion of a drug in the book does not constitute Council approval; each statement is simply the most authoritative and objective consensus the Council could obtain.

Otherwise, "New Drugs" is an entirely different book from "New and Nonofficial Drugs." Not only does it have a new format and larger scope but it is organized and oriented toward therapy to make it most useful to the practicing physician. It takes its place as a very significant part of the Council's continuing drug information program, which also includes the receipt and dissemination of adverse drug reaction reports and regular communication of drug information to the medical

(Continued on Page 24)

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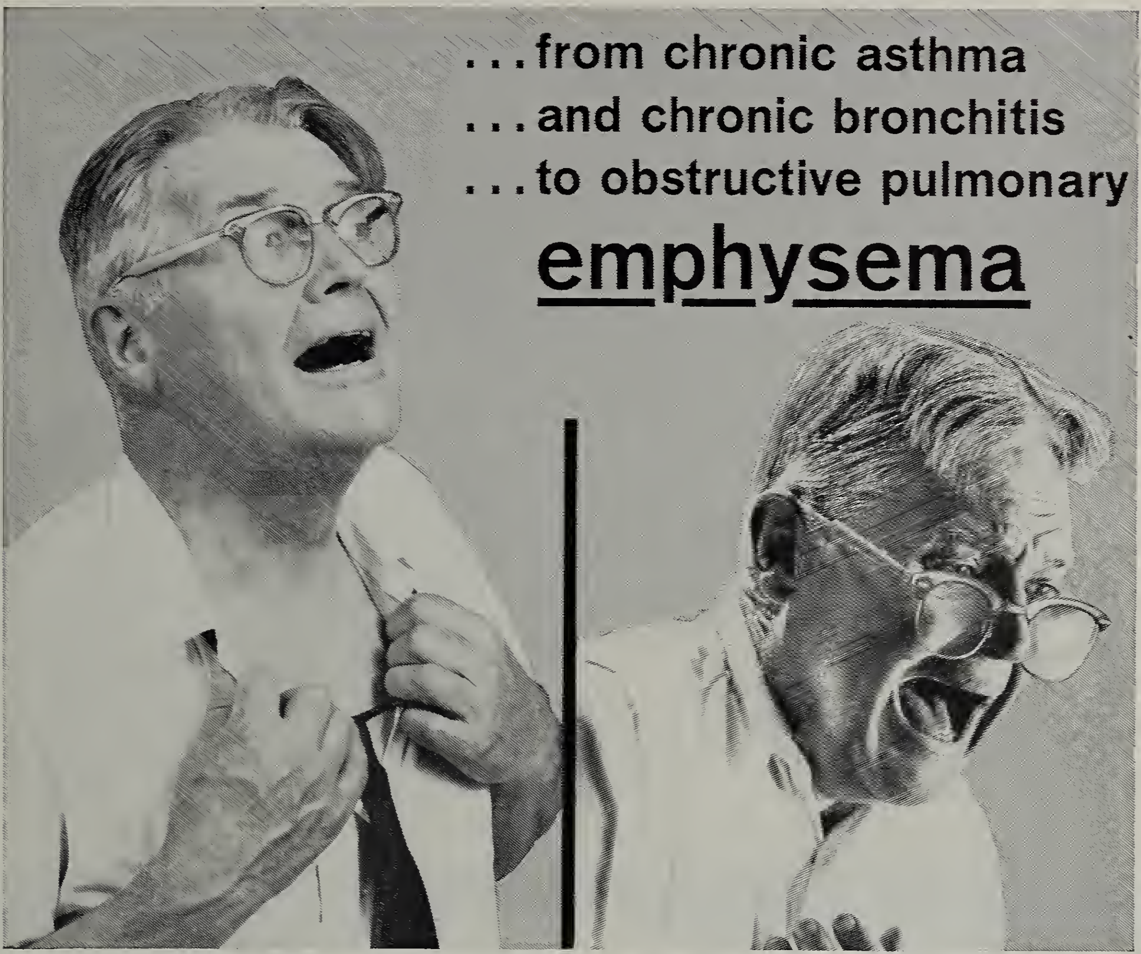

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Unusually well tolerated. Does not contain adrenergics. May be contraindicated in peptic ulcer and gout.

1. Boren, H. G.: M. Clin. North America 43:48 (Jan.) 1959.
2. Jackson, R. H., et al.: Dis. Chest 45:75-85 (Jan.) 1964.

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AMA Book on New Drugs Designed For Physician

(Continued from Page 17)

profession through articles in the *Journal of the American Medical Association.*

The book is organized into chapters and sections based, insofar as possible, on therapeutic uses of the new drugs rather than their chemistry and pharmacology. Each chapter or major section is prefaced by an introductory statement that discusses the relationship of the drugs to each other and to older drugs.

New drugs are described in monographs that give the adopted nonproprietary name, chemical or biological identity, actions and uses, limitations, adverse reactions, precautions, dosage and routes of administration, preparations and their available sizes or strengths, known sources of supply together with the commercial name or names by which the drug is sold in the U.S., year of commercial introduction in the U.S., year of evaluation for "New Drugs" or "New and Nonofficial Drugs," and year of the most recent revision of the Council-sponsored monograph.

All drug monographs are revised whenever the Council feels that re-evaluation of a drug's status is necessary on the basis of significant new information.

An example of the information furnished by "New Drugs" are these excerpts from the chapter on analgesic (pain-relieving) drugs:

"Analgesics," explains the introduction to the chapter, "act centrally to relieve pain without causing loss of consciousness. They may be broadly classified as addicting (potent) or nonaddicting (mild) pain relievers.

"The addicting analgesics not only raise the threshold of pain perception, but also suppress the patient's natural tendency to react to severe pain with alarm and apprehension. Drowsiness and euphoria are often components of their analgesic action, and they may produce tolerance and psychogenic and physical dependence (addiction).

"The nonaddicting drugs may act by raising the threshold of pain perception; some of them also possess certain peripheral actions that aid in reducing pain arising in somatic structures such as joints and muscles. These analgesics are effective mainly in patients with mild to moderate degrees of pain, and they act without causing appreciable sedation or euphoria."

Following the introduction is a listing of addicting and nonaddicting analgesics, discussions of the general uses, adverse reactions and precautions attendant to each class of analgesic drugs and monographs that discuss separately each new analgesic marketed within the past 10 years.

Plans call for updating of "New Drugs" annually, with future editions to appear no later than April 1.

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One or two capsules every four hours.

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Vitamin B_6 (pyridoxine HCl, U. S. P.)	0.5 mg.
Niacinamide, U. S. P.	50 mg.
Calcium pantothenate, U. S. P.	5 mg.
Vitamin E (from alpha tocopherol acetate)	5 I.U.
Rutin, N.F.	5 mg.
Cobalt (from cobalt sulfate)	0.033 mg.
Molybdenum (from sodium molybdate)	0.066 mg.
Copper (from copper sulfate)	0.33 mg.
Manganese (from manganese sulfate)	0.33 mg.
Magnesium (from magnesium sulfate)	2 mg.
Iodine (from potassium iodide)	0.05 mg.
Potassium (from potassium sulfate)	1.66 mg.
Zinc (from zinc sulfate)	0.4 mg.
(2) Hematopoietic Factors	
Iron (from ferrous sulfate)	3.40 mg.
Vitamin B_{12} (cobalamin concentrate, N.F., as Stablets®)	1 mcg.
Vitamin C (ascorbic acid, U. S. P.)	50 mg.
(3) Digestive Enzyme	
Pancreatic substance*	50 mg.
(4) Gonadal Hormones	
Methyltestosterone	1.0 mg.
Ethinyl estradiol	0.006 mg.
(5) Amino Acids	
L-lysine	50 mg.
Glutamic acid	30 mg.

*Enzymatically active defatted material from 250 mg. of whole fresh pancreas.

Precautions: Contraindicated in patients in whom estrogen or androgen therapy should not be used, as in carcinoma of the breast or prostate.
Dosage: One capsule, t.i.d. with meals, or as directed by physician.
Supplied: Bottles of 60 capsules. Rx only.
References: 1. Dufficy, R. G., Jr.: J. Am. Geriatrics Soc. 5:936 (Nov.) 1957. 2. Ende, M.: Southwestern Med. *38*:625 (Oct.) 1957.

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Aspirin Poisoning Can Be Stopped

If a small child suddenly begins deep breathing or vomiting or seems lethargic and confused, he may have swallowed too many aspirin tabets.

Children sometimes swallow aspirin accidentally, but parents are too-frequently guilty of carelessly giving them overdoses, said an article in the May 31 *Journal of the American Medical Association.*

Parents should learn that not every fever needs to be combated with aspirin, and that the small child should not be given aspirin except at the direction of a physician, wrote Alan K. Done, M.D., of the Department of Pediatrics, University of Utah College of Medicine, Salt Lake City. Dr. Done is a member of the Household and Economic Chemicals Panel of the AMA Registry on Adverse Reactions.

Aspirin (sodium salicylate) and oil of wintergreen (methyl salicylate) are the most important causes of accidental poisoning in children, the article said. The salicylates also are frequently chosen by adults for suicide attempts.

The aspirin-substitutes, salicylamide and acetaminophen, produce another type of poisoning, and were not discussed in this article.

Aspirin is the most commonly involved, but oil of wintergreen accounts for a disproportionately high number of deaths, the article said. As little as one teaspoonful can be fatal.

Early symptoms of salicylate poisoning include vomiting, ringing in the ears, unusually deep breathing, fever, lethargy, and mental confusion. In severe poisoning, convulsions, coma, and respiratory or cardiovascular failure may occur.

"The most severe instances of aspirin poisoning among young children result from therapeutic overdosage," Dr. Done said.

Because many parents are not aware of the different sizes, an infant sometimes is given children's (1¼ grain) or even adults' (5 grain) aspirin tablets instead of baby aspirin (½ grain).

"Since giving aspirin every four hours to a young child can result in gradual accumulation of toxic levels, administration should be no more frequent than every six hours. An adequate fluid intake also is important," Dr. Done said.

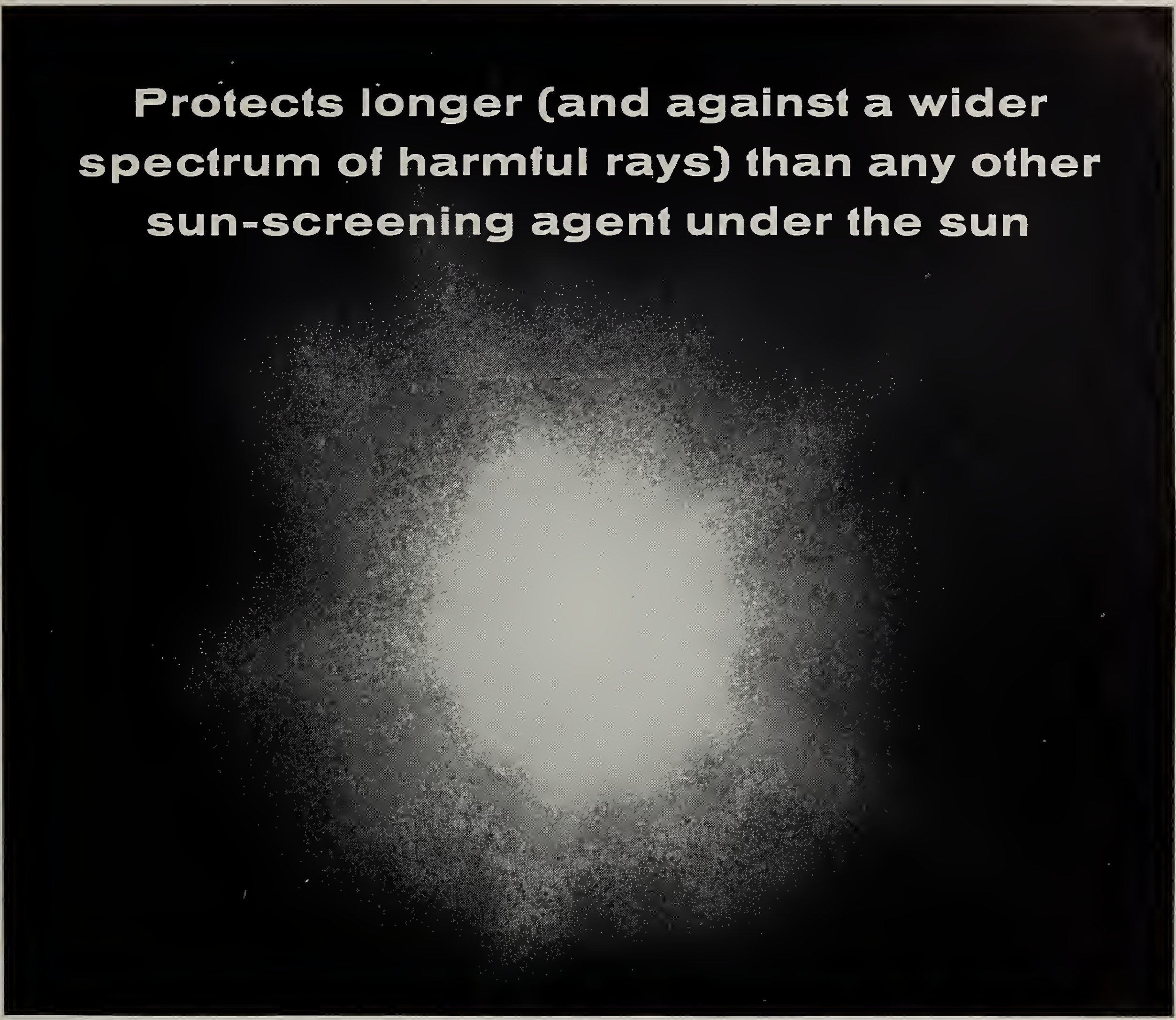
In case of an overdose, sodium bicarbonate (baking soda) should not be given as a remedy. Soda may speed the body's absorption of the poison, the article said.

The first and most important step is to take the victim to a doctor.

The article also suggested packaging of aspirin in smaller containers, such as two-tablet cellophane or foil packages.

"Accidental poisoning occurs most commonly when salicylate has been removed from its usual

(Continued on Page 32)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Aspirin Poisoning Can Be Stopped

(Continued from Page 30)

storage place. Thus, a locked or inaccessible medicine cabinet solves only part of the problem. Parents must realize the importance of not leaving such a potentially toxic material out of their sight, even for an instant, until it has been returned to safe storage," Dr. Done said.

The dangers of flavored aspirin have been mentioned often, Dr. Done said, but many cases of severe poisoning involve unflavored preparations.

"Because of the extreme toxicity of oil of wintergreen, the surest means of preventing poisoning from this substance is to discourage its presence in the home," he said.

Complex acid-base disturbances may result from salicylate poisoning. The article outlined diagnostic and treatment procedures for physicians.

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Combat Fatigue Lives On

It has been 20 years since they came home, but many World War II veterans still experience the sweaty hands, the jumpiness and the nightmares they acquired with combat fatigue.

Instead of fading away, these symptoms may be becoming more severe as the men get older, suggested a report in the May *Archives of General Psychiatry,* published by the American Medical Association.

Combat fatigue sufferers were found to overreact to sounds of airplanes, firecrackers, cap pistols and other loud noises, and to combat scenes in movies or TV. Some were irritable, easily tired, or experienced memory and concentration difficulties.

"Combat fatigue syndrome expresses itself not only in symptoms and worries, but in impaired efficiency and morale," said the report by Herbert C. Archibald, M.D., chief of the mental hygiene clinic of the Oakland, Calif., Veterans Administration Hospital, and Read D. Tuddenham, Ph.D., professor of psychology at the University of California, Berkeley.

"Three quarters (of a group studied) reported that there were periods when their symptoms interfered with providing for their families, and that they had given up hobbies they had previously enjoyed. Almost half reported that their sex lives were unsatisfactory and they were unduly irritable with their children. More than a third were unemployed at the time of our survey," the report said.

The investigators studied 157 combat veterans of World War II and the Korean War, including combat-fatigue victims undergoing psychiatric treatment, psychiatric patients who had not been in combat, and control groups of veterans who had been in combat but were not psychiatric patients and apparently had made an adequate postwar adjustment.

The men most often disturbed seemed to be "loners" who avoid communication and expression of feeling, the report said.

Combat fatigue sufferers may have been susceptible to stress before they went to war, the report said. However, there is no way now to measure that susceptibility or the stress inflicted by combat.

"Meanwhile, we are faced with a human problem. There is a large and growing number of victims of the war who need help, but whose problems are still not even recognized," the report said. "If we are to improve our methods for treating them, we must at least find and keep track of them."

California
Medicine

Immunization Against Viral Diseases

PAUL F. WEHRLE, M.D., *Los Angeles*

■ *Means are now at hand, if properly employed, to virtually eliminate clinical poliomyelitis and measles from this country. If such control is to be accomplished, more effective means are required to reach virtually all of the four million infants born each year in this country. Influenza can be suppressed, and improvements in influenza vaccine have been achieved in recent years.*

It seems likely at this time that at least several of the more important viral diseases can be controlled by utilizing antigens based on the biologic characteristics of the agent, and directed toward the reservoir of infection and the conditions favoring transmission of the infection.

The theoretical problem of the effects in man of viruses that are oncogenic in rodents and are derived from various tissue culture systems deserves serious attention. However, this consideration, that of antigenic potency, and other problems reviewed should not be allowed to subvert efforts to solve the real problems that face us, the disability and death resulting from these common infections.

EFFECTIVE CONTROL of infectious disease remains a problem of major importance. Despite the availability of numerous antigens and virtually complete control, at least in this country, of the classic plagues of mankind, infectious disease still accounts for a major portion of absenteeism in industry and schools and remains a significant cause of death.

It is the purpose of this communication to review the present status of immunization against various viral diseases. Many methods of appraising the extent of the task ahead have been employed. The excellent data on family illness accumulated by Dingle and his colleagues at Western Reserve University, data concerning the causes of school absenteeism at various ages, illnesses in industry and the many careful studies done in military populations have defined certain types of disease and their relative importance under certain conditions.

To those of us associated with hospitals it is apparent that our limited hospital resources are often stretched to the breaking point by variations in the prevalence of various communicable diseases. As noted in Table 1, infectious disease accounted for more than half of the total admissions to the Children's Division during the four months preceding the preparation of this manuscript. If one subtracts the 622 admissions to the Communicable Disease Service from this total and considers the Pediatric Service alone, 1,098 of 2,511

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TABLE 1.—*Admissions to Children's Division Los Angeles County General Hospital November 1964-February 1965*

Diagnostic Category	*Numbers Admitted in Four-Month Period*				
	November	*December*	*January*	*February*	*Total*
Bronchiolitis	22	31	119	184	356
Croup and LTB	43	23	13	19	98
Pneumonia	59	80	135	149	423
Communicable Disease Service	142	180	167	133	622
Misc. Infections	54	50	66	51	221
Non-Infectious	290	391	399	333	1413
Total	610	755	899	869	3133
Per Cent Infectious:	52.5	48.2	55.6	60.8	54.9

admissions or 43.7 per cent were for various infectious disease problems. Even more important, during this four-month period there was an increase of more than 800 per cent in one specific clinical disease entity, bronchiolitis, which involves young infants almost exclusively. Admissions increased from 22 in November to 184 in February, 1965. This increase has been confirmed as again associated with respiratory syncytical virus,* an agent commonly associated with this illness in infants and young children on our service as elsewhere. This illness is not simply a nuisance; five of the patients admitted for acute bronchiolitis (or over 1 per cent) died (Table 2). In passing, it is apparent that various infectious diseases were responsible, at least in part, for 49 of 72 (68 per cent) of all deaths excluding newborns on our combined Communicable Disease and Pediatric Services during this period, and for 20 of 45 (45 per cent) of deaths on the Pediatric Service alone.

While it is apparent that the majority of deaths from infectious diseases are due to bacteria, the importance of viral disease as a cause of morbidity and mortality is apparent. In addition, data on animals[24] and on infants[5] support the concept of bacterial-viral synergism as a mechanism of disease production. Careful studies to further establish the observation of Mathies[16] indicating wide seasonal variations in *H. Influenzae* meningitis mortality and the mechanism underlying the well known increased incidence of meningococcal disease in military recruits and bacterial pneumonia in young adults seen during influenza virus outbreaks, may be helpful in further defining the role, and subsequent control, of viral infection in the incidence, pathogenesis and virulence of bacterial disease.

Approaches for Control

For adequate control of viral infection three approaches seem possible. The first, active immunization, appears to be the most promising at the present time. The second, an alteration of host defenses, is at least a theoretical possibility. Chemoprophylaxis, the third, is an interesting concept and recent work utilizing chlorguanide in prophylaxis of malaria indicated that effective prophylaxis for at least one year follows a single dose of this agent.[3] This suggests that effective long-term chemoprophylaxis may be a possibility with other organisms in the future. However, as a caution to hopes raised by this approach in malaria and by drugs effective against viral agents, one must recall that the most nearly ideal antibacterial agent, penicillin, has not provided the type of control we desire against even the extremely penicillin-sensitive group A streptococcus.

Nonspecific Host Factors

Even in Southern California the seasonal variation in prevalence of various communicable diseases is difficult to explain on the basis of direct influence on the parasite alone. Although it is difficult to identify individual human factors important in resistance and study them in detail, the recent recruit studies by Pierce and coworkers,[21] which have yet to be confirmed, suggest that a delay in the staging of routine immunization proce-

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*Virus isolations under supervision of Bernard Portnoy, M.D.

TABLE 2.—*Total Cases and Deaths, Children's Division Los Angeles County General Hospital November 1964-February 1965*

Diagnostic Category	*Patients Admitted to Service*			*Mortality Per Cent*
	Recovered	*Died*	*Total Admissions*	
Bronchiolitis	353	5	365	1.37
Other Respiratory	514	7	521	1.34
Communicable Disease Service	593	29	622	4.66
Misc. Infections	213	8	221	3.62
Non-Infectious	1388	25	1413	1.77
Total	3061	74	3142	2.36

dures in recruit populations was associated with a decrease of about 20 per cent in the incidence of significant respiratory disease during a ten-week training period. If confirmed, and perhaps extended by further studies of host-virus-bacterial interaction, this type of observation suggests that a technique may be at hand to evaluate specific factors in humans that may be altered by stress.

The discovery of interferon by Isaacs and Lindemann[11] offered hope that a nonspecific mechanism effective against many types of viral disease and produced by many types of host cells could be stimulated by vaccines or perhaps be supplied artificially to provide an increase in host resistance. Further studies have shown that this material is a protein produced by a wide variety of cells and in response to many types of viral infection and that it retains its activity over a wide range of pH values. It is only weakly antigenic, and thus would not be expected to be eradicated by normal host defense mechanisms. The initial hope that this interesting material would be useful in prophylaxis or therapy following stimulation by various vaccines has not been borne out by further studies with the possible exception of the transient rise following attenuated measles vaccine.[20] There seems to be little likelihood of stimulating increased production of long duration by vaccines or other techniques in the host, and commercial production of this material in the laboratory and its effective use seems most unlikely at this time. It should presently be regarded as an interesting substance illustrating one of the mechanisms of host defense against viral infection[1] and as such represents an extremely important contribution.

Active Immunizations

Vaccinia virus was demonstrated to be effective in the prevention of smallpox more than 150 years ago, and more recently several other effective vaccines were prepared either in animals or in chick embryos. The most important single discovery, the adaptation of poliovirus to tissue cultures by Enders, Weller and Robbins,[7] opened a new era in the cultivation of many viruses. This approach has led to the isolation and characterization of more than 100 viruses from the respiratory tract and a nearly equal number from the gastrointestinal tract of man alone.

Production of viruses is now possible in the absence of substantial quantities of host tissue, facilitating further purification. Equally important, the selection of virus strains from single particles for certain characteristics is also possible by altering cell types and temperature. It is now possible to characterize many viral diseases and to determine their relative importance, prevalence and extent of antigenic variation. Persistence and prevalence of circulating antibody against these agents can also be ascertained relatively easily.

As a result of both epidemiologic and laboratory investigation, it has become apparent that some types of viral infection are caused by agents of relatively stable characteristics and with long-lasting resistance to clinical reinfection. Examples of these, as suggested by Hilleman,[9] are smallpox, yellow fever, other arboviruses, measles, mumps, rubella, varicella and poliomyelitis.

It is also becoming increasingly apparent that some viruses are not associated with similar long-lasting immunity to reinfection. The respiratory virus complex, particularly some of the more recently recognized agents, appear to fit this category, with demonstrated reinfections in persons presumably immune by virtue of previous infection. The best examples of this category are the respiratory syncytial and parainfluenza viruses.[12] While, in the former group, selected attenuated strains may be most effective and offer the most reasonable approach to complete control, inactivated vaccines, particularly with adjuvants, may hold the most promise in the latter situation. It seems unrealistic to expect a selected or attenuated agent to provide more effective and durable protection than that following the natural infection with the wild agent. However, one should recall that even relatively short-lived protection, if effective, may be extremely valuable, as in the young infant against respiratory syncytial virus, or in the pregnant woman against rubella.

As in the case with other discoveries, the advent of tissue culture methods for vaccine preparation has been associated with entry into a complex field with many unknowns, still unresolved. The promises and problems in immunization against viral diseases can best be illustrated by specific examples of vaccines either now licensed or under study. The promises are apparent to all, while the problems and unknowns have involved consistency and duration of effectiveness and potency, adequate safety standards for use in man, and the presence in tissue culture systems of hitherto unrecognized latent viruses, some with oncogenic potential in animals.

TABLE 3.—*Measles and Measles Encephalitis State of California, 1955-1964 (Data from California State Department of Public Health)*

Year Reported	Measles		Measles Encephalitis		Total from Measles
	Cases	Deaths	Cases	Deaths	Deaths
1955	68,961	28	72	9	37
1956	32,741	7	52	7	14
1957	53,543	16	95	11	27
1958	36,231	7	66	5	12
1959	41,018	17	96	13	30
1960	22,648	6	68	6	12
1961	39,201	13	98	11	24
1962	28,585	9	80	5	14
1963	25,058	21	87	7	28
1964	34,451	N.A.*	83	11	(Incomplete)

*Not available.

One of the clearest illustrations of both promises and problems is that of measles virus, first isolated slightly more than a decade ago.[6] It has long been apparent to epidemiologists, and more recently to virologists, that this agent is not subject to significant antigenic variation and that naturally acquired infection is followed by life-long immunity to disease and probably to reinfection as well. The need for prophylaxis is readily apparent when one considers the severity of the illness, the frequency of bacterial complications and the occurrence of clinically apparent encephalitis in approximately 0.1 per cent of the cases. The latter is frequently followed by either motor or intellectual impairment among those who survive. Figures for California alone emphasize this need, as noted in Table 3, and it is apparent that the frequency of encephalitis, disregarding all other considerations, justifies the routine use of a preventive agent for this disease.

As with other viruses, during the attempts to prepare measles virus for vaccine development and early field trials it was discovered that at least one and perhaps several "fellow travelers" were present. These agents, known for many years as the avian-leucosis group, are viruses associated with various types of avian malignant disease and are commonly found in chickens and in the chick embryo tissue culture system used for propagation of this virus. While it is true that in the past many persons had received yellow fever vaccine contaminated with these agents without demonstrable harmful effect, these recipients were mainly adults. Since measles vaccine would be given to young children, and the young of tumor-susceptible species are less resistant than older animals, the proper decision was made to withhold vaccine licensure until assurance was gained that measles vaccine would be free of these agents.[26]

As a result of extensive trials by many investigators, both inactivated measles virus and the active attenuated Edmonston B virus were thoroughly evaluated. The latter was used alone, with gamma globulin or following one or two doses of inactivated vaccine given at monthly intervals. At present it would appear that the inactivated vaccine provides temporary resistance to disease and little protection, if any, to subclinical infection. The attenuated Edmonston B strain, when used alone, has been associated with frequent febrile reactions, and convulsions have been reported in about 2 per cent of recipients.[23] These reactions are sufficiently frequent to cause appreciable concern among parents, a concern also expressed among physicians who have recently used this strain again without gamma globulin or previous modification with inactivated vaccine.

As a result of an additional 85 passages in chick embryo tissue culture at reduced temperatures, a further attenuated virus was obtained by Schwartz.[23] This variant appears to have retained the antigenic characteristics of naturally occurring measles, the lack of infectivity to contacts of recently immunized persons and adequate antibody response characteristic of Edmonston B virus with substantially fewer febrile reactions and a lower incidence of rash when given alone.[14]

With the licensing of the further attenuated measles vaccine strain on February 7, 1965, three different vaccines are now available and at least five routines may be followed. The three vaccines are the inactivated vaccine, the Edmonston B attenuated and the further attenuated vaccine strain. While there are no known contraindications to immunization with inactivated measles vaccine, it has become apparent that the duration of immunity with the use of this vaccine alone is relatively short lived. Its only usefulness at present appears to be in pregnant women who have not had measles previously, in persons undergoing steroid therapy or in children with leukemia or similar blood dyscrasias—situations in which attenuated measles vaccine is contraindicated. In the latter situation it would be particularly desirable to have data concerning the results of subsequent chance natural measles exposure in leukemic children, since inactivated vaccine does not prevent subsequent infection, and infection, with serious consequences, may still be theoretically possible in immunized leukemic children. Inactivated vaccine may also be used as a means of reducing the febrile reactions of subsequent Edmonston B vaccine by giving a single dose or a series of two doses at monthly intervals before the administration of the Edmonston B attenuated vaccine one month later.

When gamma globulin is administered in doses of 0.01 ml per pound of body weight simultaneously at a separate site, the reaction rate of Edmonston B vaccine is also reduced substantially. The Edmonston B vaccine now on the market has been used extensively without gamma globulin or without previous administration of killed vaccine. An appreciable proportion, perhaps 10 per cent, of recipients will have reactions of sufficient degree to warrant at least a telephone call and frequently a visit by a physician during the height of the reaction. While these reactions may be a nuisance and probably will preclude the widespread use of this vaccine alone in public clinics, they are of little real significance.

The recently released further attenuated virus, developed after additional passages of the Edmonston B strain at low temperature, would appear to resolve the problem of either giving multiple injections or risking the alternative, an excessive rate of reaction among recipients. In Table 4 data are presented which indicate the comparative reaction rates with the various alternate regimens listed above. Clearly, in terms of reaction rate alone, there is little difference as between the use of the further attenuated vaccine alone, the simultaneous administration of gamma globulin and Edmonston B, and the use of preparatory inoculation with inactivated vaccine followed in one month by the Edmonston B.

TABLE 4.—*Reactions Following Various Methods of Measles Immunization (Data from Krugman and Coworker[14])*

Type of Vaccine	*Symptoms (Per Cent)* Fever 103° +	*Symptoms (Per Cent)* Rash	*Total Studied*
Edmonston B	30	50	175
Edm. B + Gamma Globulin (0.01-0.02ml/lb.)	15	12	854
Further Attenuated	15	5	569

An interesting facet of the exploration of attenuated measles virus is the complete absence of transmission to susceptibles exposed to immunized children and its very low infectivity, even when we administered it by aerosol directly into the respiratory tract at times of high prevalence of measles. This characteristic is in sharp contrast to the behavior of the natural disease. In addition, although highly infectious parenterally, the infectivity is not reduced by previous experience with inactivated vaccine, a finding similar to that in polioviruses. However, in contrast to polioviruses, small quantities of gamma globulin when administered before inoculation with attenuated measles vaccines prevent effective immunization. Maximal effectiveness of attenuated vaccine is not reached until the child is 12 months of age, presumably due to traces of maternal antibody still remaining in the infant, although at least 70 per cent of infants will respond at nine months of age. While it may be desirable in periods of high measles endemicity to administer attenuated measles vaccine as early as nine months of age, it should be noted that immunization is more effective (approaching 100 per cent) at and after one year of age.

Since this year, as previously, we have seen severe measles encephalitis follow natural exposure and the use of gamma globulin to modify the disease, we feel strongly that if exposure is known, measles should be prevented by the use of a larger preventive dose of gamma globulin, and then attenuated vaccine should be given at least two months later. If the precise day of exposure is known, an alternate approach is active immunization with attenuated vaccines, providing not more than two days has elapsed.

Although long-term data concerning resistance to infection following immunization with the attenuated viruses are not yet available, and will not become available for many years, antibody titrations following the administration of these vaccines are shown in Chart 1. While antibody titers following the administration of the further attenuated vaccine may not appear to persist at levels as high as in the case with Edmonston B or natural measles, they far exceed that necessary to prevent clinical measles, and failures in protection with either vaccine have been rare. Even if complete decay of circulating antibody should occur, it is likely that recall of immunity will be rapid and

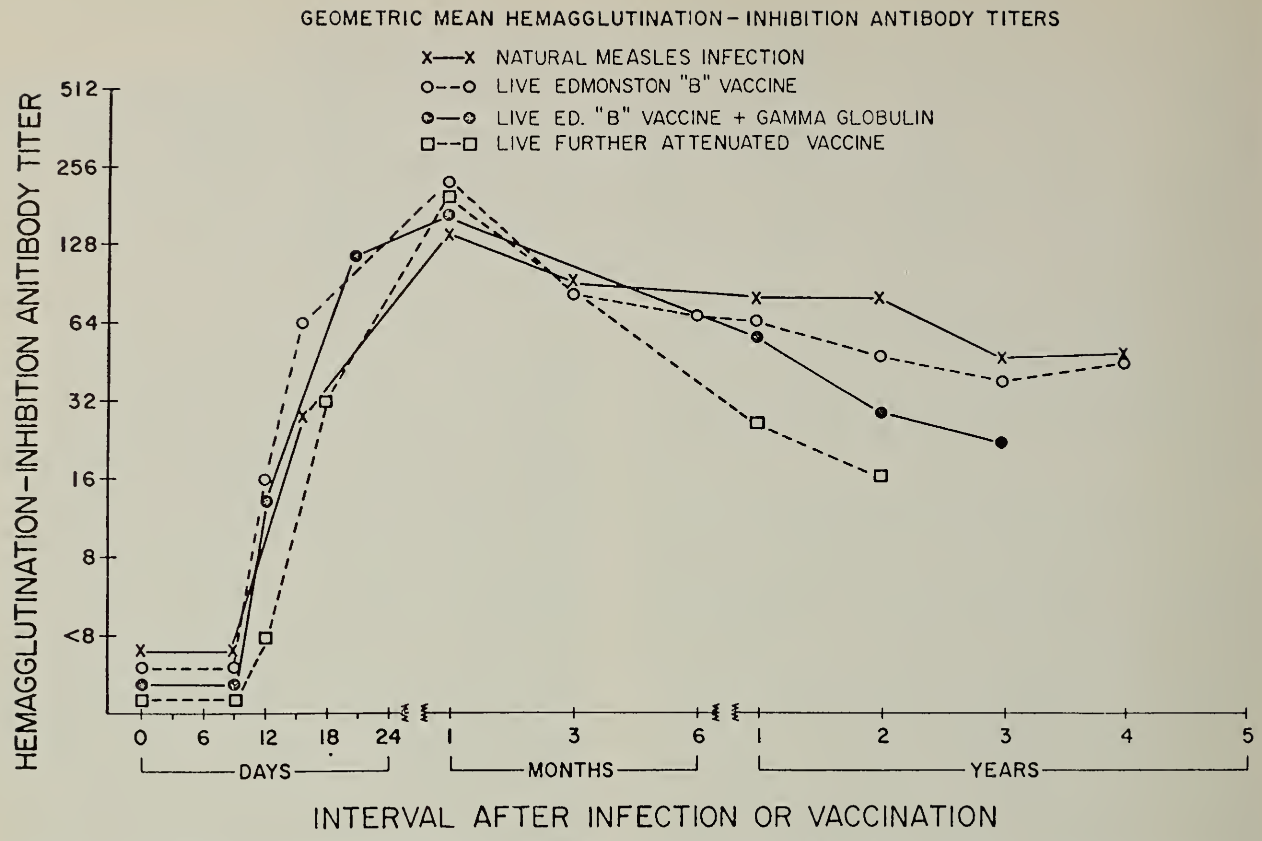

Chart 1.—Measles Antibody Response and Persistence Following Natural Infection and Vaccination. (From Comparison of the Pattern and Persistenc of the HI Antibody Response Following Natural Infection and Vaccination in Krugman, S., and Ward, R., Infectious Disease of Children, 3rd Ed., C. V. Mosby Co., 1964, page 136.)

clinical symptoms absent. In any event it seems apparent that any of these attenuated vaccine routines, if followed in infants one year of age and older, will be associated with extremely long-lasting if not permanent immunity to this disease.

No infectious disease has been brought under as prompt and effective control as has poliomyelitis. In 1964 only 121 cases, 94 of which were paralytic, were reported in the United States.[18] This incidence is less than one-fourth that of 1963, and only a single case has been reported thus far (March 20) in 1965.[19] Similar trends are seen for California in Table 5. It is of considerable importance that the usual seasonal increase in late summer and autumn was absent for the first time in 1964, suggesting either virtual absence of susceptible persons in the American community (a fact not borne out by numerous surveys) or profound interference with the transmission of this virus among infants and children, the well demonstrated reservoir of infection.

While it is possible that the striking decline in incidence from 1955 through 1961 was in part due to secular trends, changes in reporting and greater accuracy of diagnosis, over 400 million doses of inactivated poliovirus vaccine were administered during this period and without question this vaccine was mainly responsible for this decrease. Since 1961 more than 100 million doses of each of the three types of oral poliomyelitis vaccines have been distributed and more recently a considerably smaller quantity of oral trivalent vaccine.

The continued and accelerated decline during the last three years seems properly credited to the extensive use of oral vaccine. This decline in incidence occurred with decreasing use of inactivated

TABLE 5.—*Paralytic poliomyelitis, State of California, 1955-1964 (Data from California State Department of Public Health)*

Year Reported	*Total Patients*	*Rate Per 100,000*	*Deaths*
1955	1292	9.9	36
1956	1283	9.4	53
1957	291	2.1	19
1958	232	1.6	13
1959	408	2.7	20
1960	340	2.1	23
1961	75	0.5	4
1962	76	0.4	5
1963	15	0.08	1
1964	3	0.02	1

vaccine, the continued observation that approximately 20 per cent of paralytic disease reported occurred among persons who had received three or more doses of inactivated vaccine and occasional outbreaks of paralytic disease in communities relatively well immunized with inactivated vaccine.

Problems associated with the development of these poliomyelitis vaccines have been well documented[13] and require little discussion here. These include, with inactivated vaccine, difficulty in establishing adequate safety standards, with resultant paralytic disease among recipients in 1955.[15] In 1960 a relatively recently recognized virus, SV-40, was discovered in the vaccine originating from the tissue culture system, and this necessitated changes in safety testing to insure its absence. This relatively formalin-resistant virus is capable, in young rodents, of producing various malignant tumors and of transformation of human cells in tissue culture, although it must again be emphasized that no harmful effects have been noted in man. Problems of decreased immunologic potency, particularly of the type 3 component and subsequently the loss of pertussis antigenicity in attempts to combine diphtheria-pertussis-tetanus (DPT) and inactivated poliomyelitis vaccine further complicated application of this vaccine to prevention of disease.

During 1962 and subsequently, detailed records of cases of paralytic disease resembling poliomyelitis and occurring after administration of oral vaccine have been evaluated by special advisory committees to the Surgeon General of the Public Health Service. The most recent report[22] indicates that while it is not possible to prove that any individual case was caused by the vaccine, epidemiological evidence suggests that at least some cases were.

The maximum risk based on inclusion of all such possible disease associations appears to be substantially less than 1 per million doses administered, so it is not surprising that similar incidents were not seen with the Los Angeles County mass program of over seven million doses in 1962-63.[27]

Rapidly declining rates of poliomyelitis in this country during the last few years, the apparent minimal risk involved and the substantial effectiveness and both practical and theoretical advantages of oral vaccine suggest that certain changes may be desirable. During the past 18 months it has been apparent that adults remaining within the borders of the United States now have a negligible risk of naturally-acquired disease. Since the likelihood of vaccine-associated illness appears somewhat greater among adults than among young children, recent experience would suggest that widespread routine immunization of adults is no longer indicated or desirable. However, if these persons are in the armed forces, live in areas where poliomyelitis cases are occurring or travel outside this country, immunization should be provided, using oral vaccines.

The cases of two patients with paralytic poliomyelitis who were treated at Los Angeles County General Hospital in 1964 emphasize two extremely important points in the prevention of this disease. The first, an infant from Tiajuana, Mexico, with type 1 paralytic disease, indicates our proximity to areas with continued prevalence of endemic infection, and the need for immunization for persons traveling even to relatively nearby areas. The other, a fatal case of type 3 infection, occurred in an unimmunized infant residing in Los Angeles. Since four million infants are born each year in this country, attempts to reach and immunize these infants in spite of almost a certainty of increasing public apathy as the incidence of poliomyelitis decreases, presents a challenge to physician and health officer alike.

Active immunization against viral respiratory disease, utilizing both active and inactivated vaccines, has been studied for many years. Initial studies in this country with influenza[2,8] utilized active virus and this has been the principal direction of Russian investigation[28] and of limited studies in Britain.[17] Attention in this country and elsewhere has been directed toward formalin-inactivated vaccines, with or without adjuvants. A recently developed adjuvant[9] utilizing a metabolizable emulsified peanut oil has shown considerable promise in providing sustained response without the disadvantages of mineral oil adjuvants. Although the antigenic variation of influenza viruses is well known, the inclusion of recently isolated strains, with a suitable adjuvant, may provide a more dependable and effective agent in the future.

While the demonstrated potential of some adenoviruses to bring about tumors in rats[10,25] has temporarily slowed use of this antigen in man, it seems likely that this characteristic is associated with SV-40, a derivative of this virus, or similar agents present in the tissue culture system following isolation of these viruses. Present efforts involve extension of earlier studies, utilizing the ability of active adenoviruses, when administered by mouth, to establish silent infections in the intestinal tract with excellent immunologic response. Thus far, two adenoviruses, types 4 and 7, have been shown to infect simultaneously and without discernible symptoms in the recipient.[4] Further studies can be expected to include trials of inactivated adenovirus vaccines, using fractions of as well as complete virus particles, and with and without adjuvants. In addition, trials of various carefully selected active or live adenoviruses known to be free of oncogenic potential can be expected to be continued.

Other respiratory viruses currently under investigation in various laboratories include the reoviruses, parainfluenza viruses and respiratory syncytial virus, although not enough information has become available as yet to assess the likelihood of success in the prevention of these infections by either inactivated or attenuated viral antigens. In addition, more information is needed concerning the relative importance of these agents as well as the large number of rhinoviruses which also have been associated with respiratory illness. It is apparent also that additional ecologic information concerning these agents is needed, and also more information on their potential role in the pathogenesis of some bacterial diseases.

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Chronic Meningococcemia

Epidemiology, Diagnosis and Treatment

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■ *This report describes four cases of chronic meningococcemia with the characteristic manifestations of recurrent episodes of fever, chills, night sweats, headache and anorexia, associated with skin rash and arthralgias. The diagnosis was established in all instances by blood culture. Administration of sulfonamides in three cases and penicillin in the fourth resulted in prompt recovery. The recent finding of a strain of sulfonamide-resistant meningococci, however, indicates that antibiotic-sensitivity tests should be carried out in all cases of meningococcal disease. While waiting for the results of such tests to be reported, the clinician should initiate treatment with large doses of a sulfonamide and penicillin in combination.*

SULFONAMIDES have been used successfully in the treatment and prophylaxis of meningococcal infections since the beginning of World War II. In 1963, however, Millar and associates[10] reported the first cases of infection with a strain of sulfonamide-resistant meningococci, which had been discovered in recruits at the San Diego Naval Station in March of that year. In June, 1963, a young man with chronic meningococcemia was admitted to the University of California Medical Center. In view of the finding of Millar and coworkers, this case and three other cases of chronic meningococcemia observed at the Medical Center since 1937 were reviewed. This report describes the characteristic clinical and laboratory features in the four cases and discusses the problems of diagnosis and treatment of this relatively rare type of meningococcal infection.

Report of Cases

CASE 1. A 43-year-old man was referred to the Medical Center on June 22, 1963, because of recurrent episodes of fever (with temperatures as high as 105°F), general malaise, joint pain and headache of seven weeks' duration. At first he had been treated at home with salicylates. Then, because of repeated attacks of chills, fever and night sweats, he was admitted to a hospital in his community where laboratory tests, including blood cultures, failed to reveal any evidence of localized disease or infection. After treatment with erythromycin (Ilotycin®) for five days, he became afebrile and was discharged. Within 48 hours, fever and night sweats recurred and slightly tender red spots appeared on the legs. The spots would last several days and then regress, leaving small brownish scars. The patient continued to work but noted progressive weakness, dyspnea when climbing stairs, anorexia and a weight loss of 15 pounds. Previous illnesses included atypical pneumonia

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in 1943 and four attacks of viral pneumonia subsequently. In 1948, a submucous nasal resection had been performed.

On physical examination the patient appeared thin and chronically ill. The body temperature was 38.7°C, pulse rate 124 per minute and the blood pressure 100/50 mm of mercury. The nasal and pharyngeal mucosa appeared slightly erythematous. Several tender raised erythematous nodules, 0.5 to 1 cm in diameter, were present on the legs. Brownish areas, which were not depressed, were noted at the site of healed lesions. The cervical, axillary, epitrochlear and inguinal lymph nodes were slightly enlarged. The hematocrit was 43 per cent. Leukocytes numbered 9,740 per cu mm; the differential count showed 87 per cent polymorphonuclear granulocytes, of which 5 per cent were band forms. Results of urinalysis were within normal limits. Four days after admission, the leukocyte count was 15,900 per cu mm, with 80 per cent neutrophils. Spinal fluid obtained by lumbar puncture was within normal limits. Three blood cultures and a nasopharyngeal culture were positive for *Neisseria meningitidis,* type A. Culture of a fresh skin lesion was sterile.

The patient was given sulfadiazine orally in a dose of 1 gm every six hours. Within 24 hours he was afebrile and showed symptomatic improvement. The treatment was continued for ten days. On subsequent follow-up examination he was in good health.

Case 2. A 31-year-old man was first seen in the outpatient clinic of the Medical Center on April 7, 1944, three days before admission to the hospital. The illness had begun on February 16, with chills, fever and general malaise which lasted three days and confined him to bed. Since that time the symptoms had recurred about twice a week. The fever was associated with night sweats, headaches, vague pains in the legs and the appearance of tender raised red spots on the arms and legs. The spots, which were not pruritic, would disappear only to reappear with the next attack of fever. Anorexia developed and body weight decreased 14 pounds.

At the time of admission on April 10, 1944, the patient appeared chronically ill. The temperature was 36.5°C, the pulse rate 86 per minute and the blood pressure 100/70 mm of mercury. Erythematous maculopapular eruptions were present on the legs and thighs and both arms. The lesions ranged from 3 mm to 3 cm in diameter and were slightly tender. A short systolic murmur was audible at the mitral area. Different examiners noted that the spleen tip was palpable at times. The initial leukocyte count was 7,200 per cu mm, with 64 per cent neutrophils and 10 per cent band forms; the hemoglobin was 13.5 gm per 100 ml. Urinalysis showed no abnormality. Five days later, the leukocyte count was 10,000 per cu mm, with 76 per cent neutrophils and 10 per cent band forms. The spinal fluid (protein content, 20 mg per ml) was within normal limits. Blood cultures were positive for *N. meningitidis,* type I.

The patient was given sulfadiazine orally in an initial dose of 4 gm, followed by 1 gm every four hours for nine days. Within 24 hours the temperature dropped from 38.7°C to 36.8°C. The patient remained well thereafter.

Case 3. A 35-year-old man was admitted to the Medical Center on November 22, 1947, because of chills, fever and general malaise of 18 days' duration. The initial attack was characterized by sudden weakness, malaise and feverishness, followed in 36 hours by a brief shaking chill. Subsequently the patient had fever, with temperature rises as high as 104°F, in two- or three-day cycles separated by two-day afebrile periods. Four days after the initial episode a transient "red rash" appeared on the trunk, arms and legs. The patient also noted pain and stiffness of the ankles, knees, and wrists, aching in the calves and forearms, headaches and anorexia. He lost 30 pounds of weight in 18 days.

On physical examination the patient had red macular lesions, 10 mm in diameter, scattered over the trunk, arms and legs. Some of the lesions had red, punctate centers. The temperature was 37.2°C, the pulse rate 84 per minute and the blood pressure 128/90 mm of mercury. Coarse rhonchi and wheezes were audible at the base of the left lung. The initial leukocyte count was 16,400 per cu mm, with 78 per cent neutrophils, of which 48 per cent were nonfilamented. Hemoglobin content was 14.7 gm per 100 ml. The urine gave a positive reaction for glucose and one-plus reaction for acetone. The spinal fluid contained 65 mg of protein per 100 ml but was sterile on culture. Four blood cultures were positive for *N. meningitidis.*

The patient was given 50,000 units of penicillin G intramuscularly every three hours until he had received a total dose of 2.6 million units. He became afebrile within 24 hours. At the time of discharge on December 4, 1947, he felt well. Urinalysis at that time showed no abnormalities.

CASE 4. A 38-year-old man, living in New York City, had a "runny" nose, sneezing, sore throat, fever and a slight headache on September 6, 1956. By September 13 the symptoms had cleared almost entirely and he boarded a bus for San Francisco. Two days later, he had shaking chills, sweats, weakness, and aching pains in the thighs. Between September 17 and 19, swelling and weakness of the left ankle developed, with pain in the shoulders and elbows and swelling and redness over the left elbow and the proximal interphalangeal joint of the fourth finger of the left hand. By September 21, the joint swelling had disappeared and the patient felt better. Next day, however, the fever recurred. At that time he noted a scattering of small red raised lesions over the trunk, legs and forearms. When he was admitted to the Medical Center on September 24, 1956, he had lost 13 pounds of weight.

At the time of admission, the patient walked with a limp but did not appear acutely ill. The temperature was 37°C, the pulse rate was 88 per minute and the blood pressure 120/80 mm of mercury. Swelling of the interphalangeal joint of the fourth finger of the left hand, point tenderness over the left shoulder joint and small red swellings over the trunk, arms and legs were noted. The posterior cervical, axillary, epitrochlear, inguinal and femoral lymph nodes were enlarged bilaterally. The initial leukocyte count was 9,250 per cu mm, with 55 per cent neutrophils. The next day the patient's temperature rose to 39.8°C, and the leukocyte count was 13,900 per cu mm, with 87 per cent neutrophils. Nose and throat cultures and three blood cultures were positive for *N. meningitidis*, type II. The patient was given sulfisoxazole (Gantrisin®) orally in an initial dose of 2 gm, followed by 1 gm four times daily for 14 days. Within 24 hours he was afebrile; subsequently he made an uneventful recovery.

Discussion

The natural reservoir of the meningococcus is the nasopharynx of healthy carriers.[1] A significant carrier rate can be demonstrated in the general population, and a large proportion of the population has been shown to have antibodies against the organism.[4] The meningococcus is strictly a parasite of man and, because of its sensitivity to adverse physical conditions, requires close contact between people for its spread. Chronic meningococcal infections may also be a possible source of the spread of the organism. Goldbloom, Nickman and Seidmon,[7] for example, reported both acute and chronic infections in their series of 63 cases of meningococcal infection in over one million soldiers examined between July 1942 and July 1945. Meningococcal infections, therefore, are not uncommon, and epidemics occur in both civilian and military populations. The outbreaks of meningococcal infection during World War I and II, at the San Diego Naval Station in 1963, and at Fort Ord, California, in 1964, emphasize the susceptibility of the recruit population to this organism. Aycock and Mueller,[1] however, concluded that such epidemics are primarily a reflection of the prevalence of the disease in the area from which recruits are drawn, rather than a result of their mobilization.

The chronic form of meningococcemia is relatively rare. Benoit[3] could find reports of only 148 cases of chronic meningococcal infections in the American literature. Of 63 cases of meningococcemia reported by Goldbloom and associates,[7] only five were of the chronic form of the disease. Although other reports of chronic meningococcemia are found in the literature, the majority, like the case of Briggs[2] and that of Saslaw,[12] concern a single patient.

Benoit,[3] in reviewing the findings in 148 reported cases of the disease, pointed out that chronic meningococcemia is a clinical syndrome with characteristic symptoms and signs. The manifestations in the present cases were typical, consisting of episodes of severe fever and chills, associated with petechial or maculopapular skin lesions that tended to disappear in two or three days. The joint symptoms were arthralgic except in Case 4 where the patient had what appeared to be true arthritis. Headache and loss of weight, usually associated with anorexia, were consistent findings.

In three of the cases reported here, only one blood culture was required for isolation of *N. meningitidis*, although in Case 1 blood cultures done previously at another hospital had shown no growth. In Case 3, the first two cultures grew *Staphylococcus albus*, probably as a result of contamination; subsequent cultures on four occasions were all positive for *N. meningitidis*. Nasal or pharyngeal cultures were positive in only two cases, and culture of the skin lesion was sterile in the one case in which this test was done. The leukocyte count was variable, ranging from 9,250 cells per cu mm with a normal differential to 16,400 cells per cu mm with 78 per cent neutrophilic granulocytes.

Three of the patients were treated with sulfonamides of various types administered orally. The fourth patient received penicillin parenterally in small dosage compared with the dosage schedules used today for the treatment of meningococcal meningitis.[9] All four patients responded to treatment within 24 to 48 hours and made uneventful recoveries.

Benoit,[3] in summarizing the data on 148 cases of chronic meningococcemia, noted that 15 of the patients died and that 59 had secondary complications such as meningitis, carditis, anemia, nephritis and epididymitis. These findings emphasize the seriousness of the disease and the need for prompt diagnosis and adequate therapy. The most successful diagnostic procedure is frequent and repeated blood culture. If repeated cultures are sterile but the clinical history is suggestive, determination of the titer of the specific meningococcal agglutinins in the serum[6] may be helpful. Benoit's suggestion of a therapeutic trial of sulfonamide as a final means of establishing a diagnosis of chronic meningococcemia has, of course, been weakened by the subsequent report by Millar and associates[10] of the existence of sulfonamide-resistant meningococci. A therapeutic trial of erythromycin in one of the patients described in this report (Case 1) had no effect on the ultimate course of illness. The transient disappearance of fever may have been coincidental or may have represented a therapeutic effect. The development of resistance to erythromycin[8] is another possible but unproven explanation for the transient therapeutic effectiveness of this antibiotic in Case 1.

Meade[9] selected sulfonamide as the most effective chemotherapeutic agent for the treatment of meningococcal meningitis and suggested that blood sulfonamide levels should be determined during the course of therapy. Sulfonamide alone, however, may be inadequate for the treatment of acute or chronic meningococcal disease, particularly if the organism is resistant to the drug. The emergence of sulfonamide-resistant strains of *N. meningitidis*[10] has once again complicated the problem of therapy. To date, penicillin appears to be an effective agent against the resistant strains of *N. meningitidis* that have been isolated.[10,13] Whether penicillin should be used in all cases of meningococcal infections, either alone or in combination with a sulfonamide, will require further study. In any event, whenever meningococci are isolated, antibiotic sensitivity tests[5,11] should be done as a guide to therapy. Treatment, however, must be instituted promptly. The clinician should therefore administer a combination of a sulfonamide and penicillin in large doses until the results of sensitivity tests are reported. Such a combination may also be the treatment of choice in cases in which the diagnosis is made serologically.

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Disguised Thyroid Disorders

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■ *In six cases of hyperthyroidism and two of chronic thyroiditis herein described, the initial features of the diseases were misinterpreted as attributable to other kinds of illness such as myocardial infarction, gastrointestinal malignant disease, malabsorption syndrome, psychosis, simple exophthalmos and endemic goiter. The characteristic signs and symptoms of hyperthyroidism (in six patients) and chronic thyroiditis (in two patients) were present at the outset but were not identified. Intensive questioning and alertness were required to elicit these characteristics. The symptoms improved or disappeared after the true disease was controlled.*

In the studies of these cases, the usefulness of a number of laboratory tests was illustrated—thyroid suppression studies, 4 to 6-hour and 24-hour radioactive iodine uptake, T_3 uptake by the red cells and determinations of 24-hour urine creatine, antithyroglobulin antibody titer and long-acting thyroid stimulating hormone.

The manifestations of thyroid diseases are many and varied. The term "masked hyperthyroidism" may in part be a reflection of the "masked physician" unless he uses his clinical detective abilities.

THYROID DISEASES may manifest themselves by protean signs and symptoms. Unless the physician is alert for the less common manifestations of thyroid dysfunction, the clinical features may be easily misinterpreted.

In the following illustrative cases, observed in the Thyroid Clinic at Los Angeles County General Hospital, there was a considerable variety of initial signs and symptoms referable to thyroid disease. The elucidation of these problems was aided greatly by the use and proper interpretation of appropriate tests of thyroid function, such as 6-hour radioactive iodine uptake, red blood cell uptake (T_3), thyroglobulin antibody titer, thyroid suppression studies, long-acting thyroid stimulating factor (LATS) and determination of 24-hour urine creatine.

CASE 1. A 54-year-old Caucasian woman was admitted October 15, 1963, with complaint of progressive loss of weight, weakness and intermittent episodes of diarrhea for approximately one year. On admission her weight was 65 pounds. She had obvious cachexia and pronounced wasting. The thyroid gland was palpable but not thought to be enlarged. The initial impression was of possible gastrointestinal tract malignant disease but x-ray studies, including the chest, the upper gastrointestinal tract and barium enema films, showed no abnormality. The patient continued to lose weight. Two weeks after admission, thyroid disease was suspected and the suspicion was confirmed by a 24-hour I^{131} uptake of 82 per

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TABLE 1.—*(Case 1) Laboratory and Clinical Data 54-year-old White Woman*

Initial diagnosis: Cancer of the gastrointestinal tract
Final diagnosis: Hyperthyroidism

	1963				1964
	10/15	10/29	11/26	12/18	1/6
PBI (mcg per 100 ml)		9.3	5.6		4.5
Cholesterol (mg per 100 ml)		95			221
I^{131} uptake (per cent 24 hr.)		82			
Body weight (pounds)	65	61	82	96	102½
Therapy		Methimazole Diphenhydramine Reserpine Desiccated thyroid			

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine

cent and by positive results of other tests (Table 1). Administration of methimazole (Tapazole®) was begun and the patient gained weight rapidly and became euthyroid. She received I^{131} therapy in December, 1964.

Comment. Because classic symptoms of hyperthyroidism, such as increased sweating, hyperactivity or enlargement of the thyroid gland, were not present at the time this patient was first observed, the correct cause of the loss of weight was not seriously considered until 14 days had elapsed. Early recognition of problems of this type is important, for the situation is almost an emergency. The patients are acutely ill, are in severe negative nitrogen balance, and therapy should be begun at once.

CASE 2. A 29-year-old Negro man was admitted on June 14, 1963, with chief complaint of progressive bulging of the eyes of three months' duration. Interview elicited no mention of any recent symptoms referable to possible hyperthyroidism. No overt manifestation of hyperthyroidism was noted clinically, although some of the physicians who observed the patient considered him overly active in behavior.

On physical examination bilateral exophthalmos with moderate chemosis and infiltration was noted. The right eye was more prominent than the left. The thyroid gland was palpable but not enlarged. Results of thyroid function tests were within normal limits: Protein-bound iodine (PBI) was 7.9 mcg per 100 ml, cholesterol content was 193 mg per 100 ml and 24-hour radioactive iodine (RAI) uptake was 22 per cent. However, to fully evaluate thyroid function, a suppression study using liothyronine (Cytomel®), 75 mcg daily for one week, was carried out. The I^{131} uptake then was 21 per cent in 24 hours. A T_3 uptake test was also obtained and the value was 24.8 per cent (normal 10.3 to 14.3 per cent). With this proof of hyperthyroidism, thyroid suppression thereby was begun with Tapazole.® When the patient became euthyroid, as determined by serial measurements of T_3 uptake, he was given a therapeutic dose of 15 millicuries of I^{131}. Eye measurements improved concomitantly with antithyroid therapy (Table 2).

Comment. The correct diagnosis of hyperthyroidism in this case required the use of the I^{131} suppression test.[2] The failure to suppress proved that the gland was functioning autonomously and independently of pituitary control.[8] The significance of the exophthalmos was then clear, and proper antithyroid therapy gave good results. The elevated T_3 uptake provided further substantiation for the diagnosis of hyperthyroidism and proved a valuable indicator of adequacy of antithyroid treatment before definite therapy with radioactive iodine. An interesting feature in this case was the change of the initially negative long-acting thyroid stimulating bioassay to positive during the course of therapy with antithyroid drugs.

CASE 3. A 67-year-old Caucasian man was admitted on September 4, 1963, with complaint of sudden onset of pain in the left side of the chest and of diaphoresis beginning 12 hours before admission. An electrocardiogram showed S-T elevations in leads II, III and AvF compatible with acute diaphragmatic myocardial infarction, myocarditis or pericarditis. Treatment for acute myocardial infarction was begun. The following day the

TABLE 2.—*(Case 2) Laboratory and Clinical Data 29-year-old Negro Man*

Initial diagnosis: Exophthalmos
Final Diagnosis: Graves' Disease

	1963						
	6/13	*6/25*	*7/31*	*8/14*	*9/11*	*10/30*	*11/7*
PBI (mcg per 100 ml)	7.9		7.3		5.3	3.8	
Cholesterol (mg per 100 ml)	193		193		198	248	
I^{131} uptake (per cent 24 hr.)	22						55
Liothyronine Suppression (per cent 4 hr.)			10				
(per cent 24 hr.)			21				
T_3 uptake (per cent)	24.8			19.4	15.2		15.4
LATS			Negative			Positive	
Exophthalmos Measure—Right eye		22	20	19			
Left eye		22	20	19			
Therapy		Diphenhydramine Methimazole Desiccated thyroid					15 Mc I^{131}

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine
T_3=triiodothyronine
LATS=Long acting thyroid stimulating factor

sinus rhythm changed to an uncontrolled auricular fibrillation. This persisted despite digitalization to the point of toxicity. The possibility of thyrotoxic heart disease was then suspected and was further supported by a more detailed history in which loss of weight for a period of six months, muscle weakness, nervousness and intolerance to heat were mentioned. A four-hour I^{131} uptake of 58 per cent confirmed the diagnosis. Thereupon antithyroid therapy and sedation were begun, and within 48 hours the cardiac arrhythmia had been converted to a regular sinus rhythm. Electrocardiograms thereafter showed no further evidence of cardiac disease. Serial serum enzyme studies, glutamic oxaloacetic transaminase (SGOT) and lactic dehydrogenase (SLDH) were entirely within normal limits. Before treatment the PBI was 13.6 mcg per 100 ml. While receiving therapy the patient rapidly gained 30 pounds and was able to have radioactive iodine treatment on October 22, 1963. At last report he was well maintained on 0.2 gm of desiccated thyroid daily (Table 3).

TABLE 3.—*(Case 3) Laboratory and Clinical Data 67-year-old White Man*

Initial diagnosis: Acute myocardial infarction
Final diagnosis: Thyrotoxic heart disease

	1963							1964
	9/6	*9/12*	*9/18*	*10/3*	*10/10*	*10/22*	*12/11*	*1/5*
PBI (mcg per 100 ml)	13.6			8.5	5.3		7.2	6.0
Cholesterol (mg per 100 ml)	142						241	245
I^{131} uptake (per cent 4 hr.)		58						
(per cent 24 hr.)		84				71		
Urine creatine (mg/24 hr.)		594						
Therapy		Methimazole Diphenhydramine Reserpine Desiccated thyroid				4.2 Mc I^{131}		
Body weight (pounds)			145	150	158	167	171	175

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine
Mc=millicuries

Comment. In this case, the suspected cardiac problem was quickly confirmed by the 4-hour I^{131} uptake,[5] thereby preventing a possible delay in treatment while awaiting determination of the 24-hour uptake of protein-bound iodine (PBI). It is also interesting to note the decided elevation of urine creatine (Table 3), which was indicative of pronounced muscle wasting. The urine creatine determination is occasionally helpful in diagnosis of suspected hyperthyroidism, since it is elevated when muscle wasting is associated with the disease.[7] Also it can be used as a gauge of the efficiency of antithyroid treatment.

CASE 4. A 54-year-old Caucasian woman was originally seen as an outpatient in 1958 for an enlarged thyroid gland. No symptoms or findings of hyperthyroidism were observed. The PBI value was 4.5 mcg per 100 ml at that time. The diagnosis was multinodular goiter and no therapy was given. In 1962 the patient was seen again because of complaint of nervousness and generalized weakness of six months' duration. No considerable increase in the size of the gland was noted. PBI was 4.5 mcg per 100 ml, cholesterol was 310 mg per 100 ml and radioactive iodine uptake was 49 per cent in 24 hours. Further laboratory tests included a reversed albumin-globulin ratio of 3.8:5.0 gm per 100 ml with an elevated gamma globulin fraction which, since the patient was known to be a heavy drinker, was thought to reflect alcoholic cirrhosis. A diagnosis of nontoxic nodular goiter was made and no therapy was recommended.

In September of 1963 the patient complained vaguely of general lethargy and weakness. As she appeared clinically to be hypothyroid, thyroid function tests were carried out, including antithyroglobulin titer determination. The titer was reported at 1:500,000, demonstrating that the problem was chronic thyroiditis or Hashimoto's disease. Desiccated thyroid was given, 0.2 gm daily, and the patient underwent dramatic improvement in wellbeing and vigor. Her physical appearance changed as the thyroid gland shrank in size and her weight dropped from 136 to 114 pounds. The antithyroglobulin antibody titer dropped to 1:200,000 and the PBI rose to 7.3 mcg per 100 ml (Table 4).

Comment. This patient had had hypothyroid disease at least a year before the diagnosis (as evidenced by elevated gamma globulin fraction[3]) and perhaps as far back as 1958. Unless the possibility of Hashimoto's disease is kept in mind (especially in a middle-aged woman with thyroid gland enlargement) it may be overlooked. In our own experience, the variability and the vagueness of presenting symptoms is commonplace. The protein-bound iodine and the radioactive iodine uptake can be high, low or normal, depending on

TABLE 4.—*(Case 4) Laboratory and Clinical Data 54-year-old White Woman*

Initial diagnosis: Simple goiter
Final diagnosis: Hashimoto's thyroiditis

	1958	*1962*			*1964*
	5/16	*1/3*	*9/3*	*9/18*	*1/21*
PBI (mcg per 100 ml)	4.5	4.5	5.0		7.3
Cholesterol (mg per 100 ml)		310	275		318
I^{131} uptake (per cent 24 hr.)		49		19	
Albumin/Globulin ratio		3.8/5.0			
T_3 uptake (per cent)			13.5		
Thyroglobulin Antibody Titer			1:500,000		1:200,000
Therapy			Desiccated thyroid		
Body weight (pounds)			136		114
Serum protein electrophoresis			↑γ globulin		

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine
T_3=triiodothyronine
↑ γ globulin=increased gamma globulin

TABLE 5.—*(Case 5) Laboratory and Clinical Data 57-year-old White Man*

Initial diagnosis: Involutional psychosis-paranoia
Final diagnosis: Hyperthyroidism

	1963				
	8/21	*8/26*	*9/4*	*11/10*	*12/2*
PBI (mcg per 100 ml)	13.7	12.0	10.0	5.2	
T_3 uptake (per cent)	20.9	17.2	14.5	14.0	
I^{131} uptake (per cent 24 hr.)	54				58
Body weight (pounds)	145	154	159		
Therapy	Methimazole Diphenhydramine Desiccated thyroid				

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine
T_3=triiodothyronine

the stage of the disease. Diagnosis depends on demonstration of an elevated antithyroglobulin antibody titer and/or biopsy.[6]

In the foregoing case the morbidity of the disease increased because of delay in diagnosis that might have been made earlier had there been complete diagnostic workup and awareness of the possibility of this condition in this patient.

CASE 5. A 57-year-old Caucasian farmer was brought by his family to the Psychiatric Unit of Los Angeles County General Hospital on August 6, 1963. For the past year he had become increasingly unmanageable due to restlessness, agitation and hyperactivity. He occasionally became combative and his behavior was paranoid. He had twice been at Camarillo State Hospital for alcoholism. After psychiatric evaluation, he was admitted to the ward with a diagnosis of involutional psychosis with paranoid tendencies. On the ward his hyperactivity was quite evident, as he helped the personnel mop floors, wash windows and bus trays. He rarely slept and was constantly asking for extra portions of food. After two weeks of this behavior, a member of the ward staff suspected thyroid disease. Tests done then showed PBI of 13.7 mcg per 100 ml and radioactive iodine uptake of 54 per cent.

The patient was then transferred to the medical division and administration of methimazole (Tapazole®) was begun. He rapidly gained weight and the hypermetabolic state diminished to the point that he could be discharged for observation as an outpatient (Table 5).

Comment. This patient was one of two in the past two years who were seen first on the Psychiatric Ward but later were found to be decidedly hyperthyroid. The mental symptoms of these patients improved greatly with antithyroid treatment, indicating that the primary disturbance was probably owing to thyroid disease. Although the bizarre and erratic behavior of hyperthyroid patients is well known, occasionally this disturbance may still be misinterpreted as a functional rather than an organic illness.

CASE 6. The patient, a 39-year-old Caucasian woman, was admitted on August 12, 1963, with chief complaint of lachrymosis and swelling of the eyelids. She had lost some 100 pounds in nine months on a weight reduction regimen entailing 0.25 gm of desiccated thyroid daily, organic iodides, amphetamine and laxatives. On physical examination, a fine tremor of the hands was noted and her behavior was of neurotic type (which was in keeping with her behavioral history). Bilateral exophthalmosis was present, with severe chemosis and infiltration. Also noted were nodular pretibial infiltrations. Protein-bound iodine was 10.2 mcg per 100 ml, cholesterol 162 mg per 100 ml and butanol extractable iodine (BEI) 8.0 mcg per 100 ml. A four-hour I^{131} uptake was 15 per cent and the 24-hour uptake 28 per cent (Table 6).

The clinical question at this point was whether this patient's obvious exophthalmic problem was secondary to actual hyperthyroidism. The results of blood chemical content determinations could be ascribed to the long term ingestion of desiccated thyroid and organic iodides, and the clinical status of the patient could be due to psychoneurosis or the diet regimen she was following.

A thyroid suppression test with triiodothyronine

TABLE 6.—*(Case 6) Laboratory and Clinical Data 39-year-old White Woman*

Initial diagnosis: Thyrotoxicosis Factitia
vs. Graves' Disease
Final diagnosis: Graves' Disease

	1963							*1964*	
	8/12	*8/21*	*9/4*	*10/2*	*10/9*	*10/31*	*11/5*	*1/8*	*1/16*
PBI (mcg per 100 ml)	10.7			4.3	3.4		6.9		
Cholesterol (mg per 100 ml)	162			163			226		
I^{131} uptake (per cent 4 hr.)		15							
(per cent 24 hr.)		28							4
Liothyronine Suppression (per cent 4 hr.)			13						
(per cent 24 hr.)			18						
Exophthalmos Measure—Right eye			29			29			
Left eye			27			30			
Weight (pounds)	135		150				166	171	
LATS	Positive								
Therapy			Methimazole Diphenhydramine Desiccated thyroid Diuretics Topical steroids			10 Mc I^{131}	Tarsorrhaphy		30 Mc I^{131}

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine
LATS=Long acting thyroid stimulating factor

was carried out. The resultant four-hour I^{131} value of 13 per cent and 24-hour value of 18 per cent indicated autonomous thyroid gland function. A bioassay of the long-acting thyroid-stimulating factor (LATS) was obtained and found to be strongly positive. Administration of methimazole (Tapazole®) was begun. Supportive measures for the eye problem included administration of diuretic agents and topical use of an ophthalmic ointment. Exophthalmos continued undiminished and visual acuity began to decrease. For a time it was feared that corneal ulcerations would develop. Undermining her morale, these complications made the management of the thyroid disease even more difficult. Specialized therapy (reported elsewhere[1]) at last brought the eye problems and the nodular pretibial myxedema under control.

Comment. The correct diagnosis was not only helped by the thyroid suppression studies (which were discussed previously) but also by the assay of the long-acting thyroid-stimulating factor. This latter, a relatively new test, is still confined mainly to research, since it is technically difficult and prohibitively costly. McKenzie[4] and investigators have done much work on LATS and there is reasonably good evidence that it may be the long sought exophthalmic factor.

CASE 7. A 23-year-old Negro woman entered the hospital July 8, 1963, with chief complaint of rapid swelling of the neck that had begun a month before. This had been associated with several days of tenderness to palpation, the pain radiating to the angle of the jaw and ear. On physical examination diffuse enlargement of the thyroid gland was noted. The weight of the gland was estimated at approximately 100 gm. It was not tender to palpation.

Protein-bound iodine was 6.0 mcg per 100 ml, butanol-extractable iodine (BEI) 2.7 mcg per 100 ml, uptake of I^{131} was 13 per cent and of T_3 10.1 per cent. The thyroglobulin antibody titer was 1:32,800. A diagnosis of resolving subacute thyroiditis was made and the patient was discharged. As she desired surgical removal for cosmetic reasons, total thyroidectomy was done, with a preoperative diagnosis of possible thyroid carcinoma. The gross appearance of the gland at operation made the surgeon strongly suspect papillary carcinoma and plans were made to treat the patient with radioactive iodine postoperatively. However, the pathologist reported the microscopic features were those of classic Hashimoto's thyroiditis.

It was at this point that we first saw the patient, and in retrospect the clinical features and the re-

TABLE 7.—*(Case 7) Laboratory and Clinical Data 23-year-old Negro Woman*

Initial diagnosis: Subacute Thyroiditis
Final diagnosis: Hashimoto's Thyroiditis

	1963		
	7/8	7/15	
PBI (mcg per 100 ml)	6.0		Serum protein electrophoresis—increased gamma fraction
BEI (mcg per 100 ml)	2.7	2.3	Albumin: Globulin—3.7: 5.6 grams/100 ml
Cholesterol (mg per 100 ml)	173		Thymol turbidity—11 units
I^{131} uptake (per cent 24 hr.)	13	10.8	Serologic tests—VDRL positive —Kolmer positive
T_3 uptake (per cent)	10.1		TPI (Treponema Pallidum Immobilization)—negative
Thyroglobulin antibody titer	1:32,800		

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
BEI=butanol extractable iodine
I^{131}=radioactive iodine
T_3=triiodothyronine

sults of laboratory tests were entirely consistent with only one diagnosis—Hashimoto's thyroiditis. The symptoms of gland tenderness with radiation to the ear and the angle of the jaw are not typical of this disease (Table 7).

When last observed the patient was receiving thyroid replacement therapy and doing quite well.

Comment. The wide difference between the PBI and the BEI were a tip-off as to the right diagnosis.[3] In some cases of Hashimoto's disease the BEI (which measures the thyroxine alone) is lower than the PBI, since an enzymatic defect may be present, producing more monoiodotyrosine and diiodotyrosine than thyroxine and causing a higher PBI.

The increased serum globulin with elevated gamma fraction, the elevated thymol turbidity and the false positive response to a serologic test (the treponema immobilization test was negative) are all a reflection of the autoimmune process occurring in Hashimoto's disease.

TABLE 8.—*(Case 8) Laboratory and Clinical Data 58-year-old White Woman*

Initial diagnosis: Gastrointestinal malignancy
Final diagnosis: Thyrotoxicosis

	1964		
	1/30	2/1	2/18
PBI (mcg per 100 ml)		8.7	
Cholesterol (mg per 100 ml)		110	
I^{131} uptake (per cent 24 hr.)			69
Serum albumin (gm per 100 ml)		1.5	
Body weight (pounds)	88	78	67

KEY TO ABBREVIATIONS:
PBI=protein bound iodine
I^{131}=radioactive iodine

CASE 8. A 58-year-old Caucasian woman was admitted on January 30, 1964, because of peripheral edema of two weeks' duration. For about a year she had noted loss of weight and had had recurrent diarrhea. The initial diagnostic impression was that of either a gastrointestinal malignant lesion or a protein-losing enteropathic condition. On admission the patient weighed 88 pounds. Her weight decreased to 67 pounds while she was in the hospital, but the reduction was thought to be due to loss of edematous fluid. At first, investigation was focused on the gastrointestinal tract, with x-ray studies and tests of absorption adequacy. Although a PBI determination was carried out, the result, 8.7 mcg per 100 ml, was not given its proper significance until two and a half weeks later when a radioactive iodine uptake test was done and the amount absorbed was 69 per cent. The total serum albumin was 1.5 gm per 100 ml (Table 8). Because of these factors and voracious eating by the patient, the ward staff began to suspect that the loss of weight might have been due to something besides diuresis. With antithyroid therapy (Tapazole®) her weight increased but she remained in hospital because of severe malnutrition.

Comment. This was another case of hyperthyroidism in which the presenting symptom was severe loss of weight. If the decidedly low serum albumin level had been taken into consideration when the PBI result was evaluated (since it was the cause of the lower PBI value), perhaps the diagnosis would have been made earlier. We would like to stress again the need for rapid diagnosis and treatment of patients who present with such severe negative nitrogen balance. Such patients are critically ill and need prompt stemming of the disease process.

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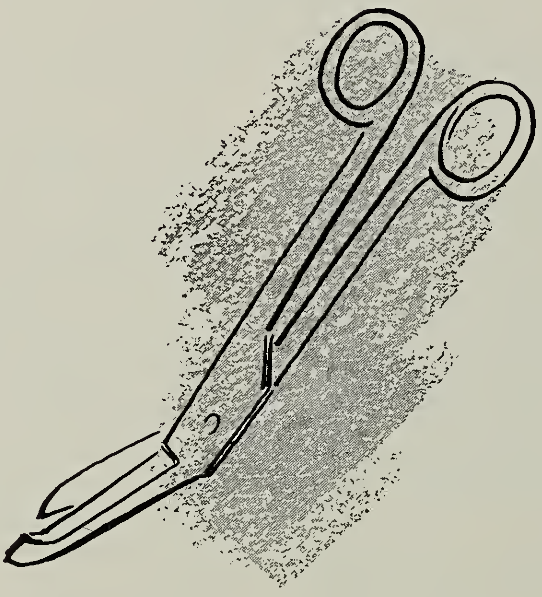

Hypertrophic Subaortic Stenosis

Clinical Recognition in Children

RALPH WEISS, M.D., *Los Angeles*

■ *Hypertrophic subaortic stenosis is a potentially serious condition which may cause sudden death. The murmur is characteristically systolic ejection and is maximal at the left sternal border. When faint, it may be confused with a non-organic murmur and when loud it may be mistaken for a ventricular septal defect or mitral insufficiency. Evidence of left ventricular hypertrophy on an electrocardiogram should alert the clinician to the possibility of this disease.*

HYPERTROPHIC SUBAORTIC STENOSIS was first described in 1957 by Brock[6] and since that time has been reported with increasing frequency. This entity is also referred to in the literature as pseudoaortic stenosis,[1] familial muscular subaortic stenosis,[5] functional aortic stenosis[10] obstructive cardiomyopathy,[9] and functional obstruction of the left ventricle.[7] The cause of the functional obstruction of the left ventricle is still controversial but appears to be related to abnormally formed muscle bundles in the region of the outflow tract. This creates a muscle "collar" during systole which impedes normal ventricular ejection and may be a cause of sudden death.

Because of the insidious onset of the disease, most cases are not recognized until school age or early adulthood. Physical findings are frequently limited to a systolic ejection murmur along the lower left sternal border which may simulate innocent murmurs or those associated with small ventricular septal defects. In some cases, the murmur is heard best at the apex of the heart and may simulate mitral insufficiency.

Although well known to cardiologists, this entity has not been adequately emphasized in the pediatric literature. The following report was selected to illustrate the difficulties commonly encountered in the recognition of this potentially serious condition.

Report of a Case

A 14-year-old Caucasian boy was admitted to the hospital on May 27, 1964, with complaint of fatigue on moderate exertion for the preceding two years. A heart murmur was known to be present since the patient was three years of age, and at 12 years a diagnosis of a small ventricular septal defect was made by a cardiologist.

The family history was striking. The patient's mother "developed heart disease at 32 years of age," and the maternal grandfather was told at the age of 20 that he had a "bad heart." In addition, a maternal aunt had had "heart trouble" since

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TABLE 1.—*Cardiac Catheterization Data*

Site	*Pressure mm of Mercury*	*Oxygen Saturation*
Superior vena cava	$\bar{X}=4$	68
Inferior vena cava	$\bar{X}=4$	73
Right atrium	$\bar{X}=4$	67, 68, 68
Right ventricle	30/6	....
Right pulmonary artery	30/15	65
Main pulmonary artery	28/17	67
Brachial artery	125/72	98
Left ventricle	120/16	97
Aorta	130/100	97
Left ventricle with isoproterenol	148/10 to 112/10	....
Aorta with isoproterenol	116/80	....

$\bar{X}$=mean pressure

childhood. Definitive diagnosis was not established in any of these persons.

Pertinent physical findings at the time of admission were limited to the cardiovascular system. There was a grade IV/VI systolic ejection murmur, best heard at the fourth interspace on the left sternal border and radiating to the apex and toward the base of the heart. A thrill was not present, but a left ventricular heave was palpated at the apex. The first and second heart sounds were normal. Blood pressure in the upper extremities was 120/74 mm of mercury and in the lower extremities 150/88 mm.

Evidence of moderately severe left ventricular hypertrophy was demonstrated by electrocardiogram (Figure 1). X-ray examination showed no abnormality (Figure 2). A phonocardiogram con-

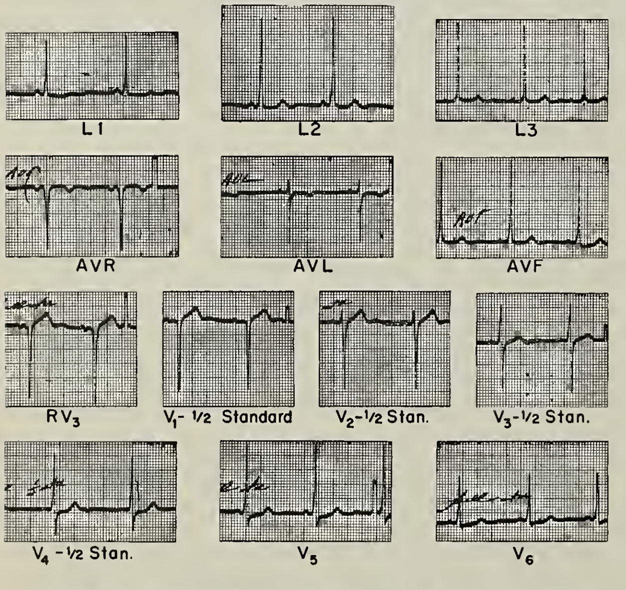

Figure 1.—Electrocardiogram showing deep S waves in AVR, V_1 and V_2, and tall R waves in AVF.

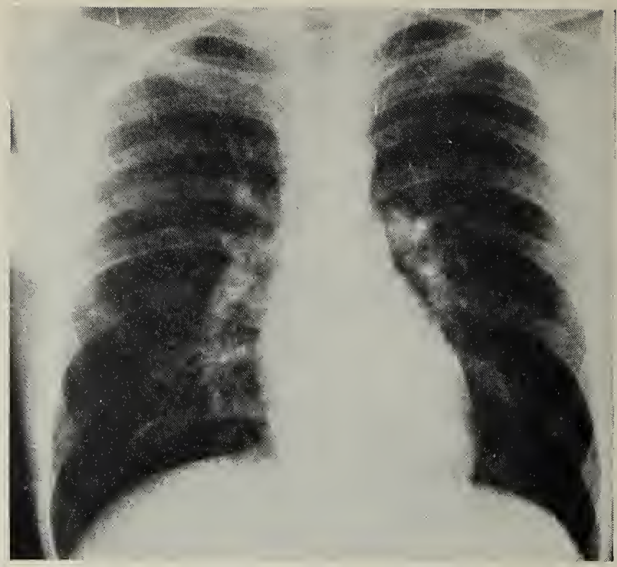

Figure 2.—Teleroentgenogram taken at time of catheterization studies. No abnormalities were noted.

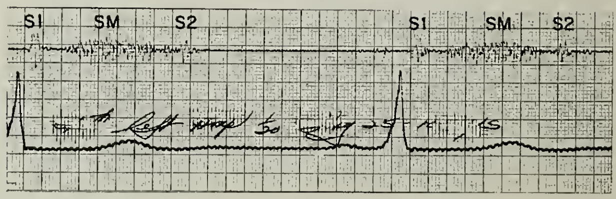

Figure 3.—Phonocardiogram at 4th interspace on left sternal border, demonstrating systolic ejection murmur (SM) between the first heart sound (S1) and the second heart sound (S2).

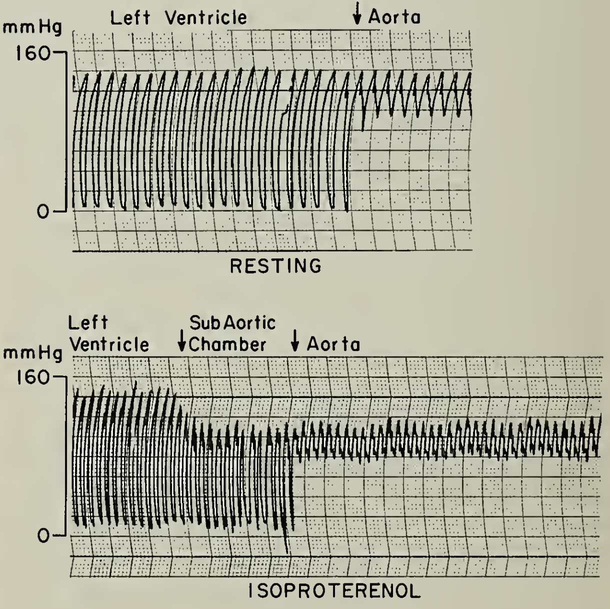

Figure 4.—*Above*, pressure tracings recorded during withdrawal of catheter from left ventricle to aorta at rest with no systolic gradient. *Lower*, withdrawal tracing during isoproterenol infusion demonstrating a systolic gradient in the subaortic region of the left ventricle.

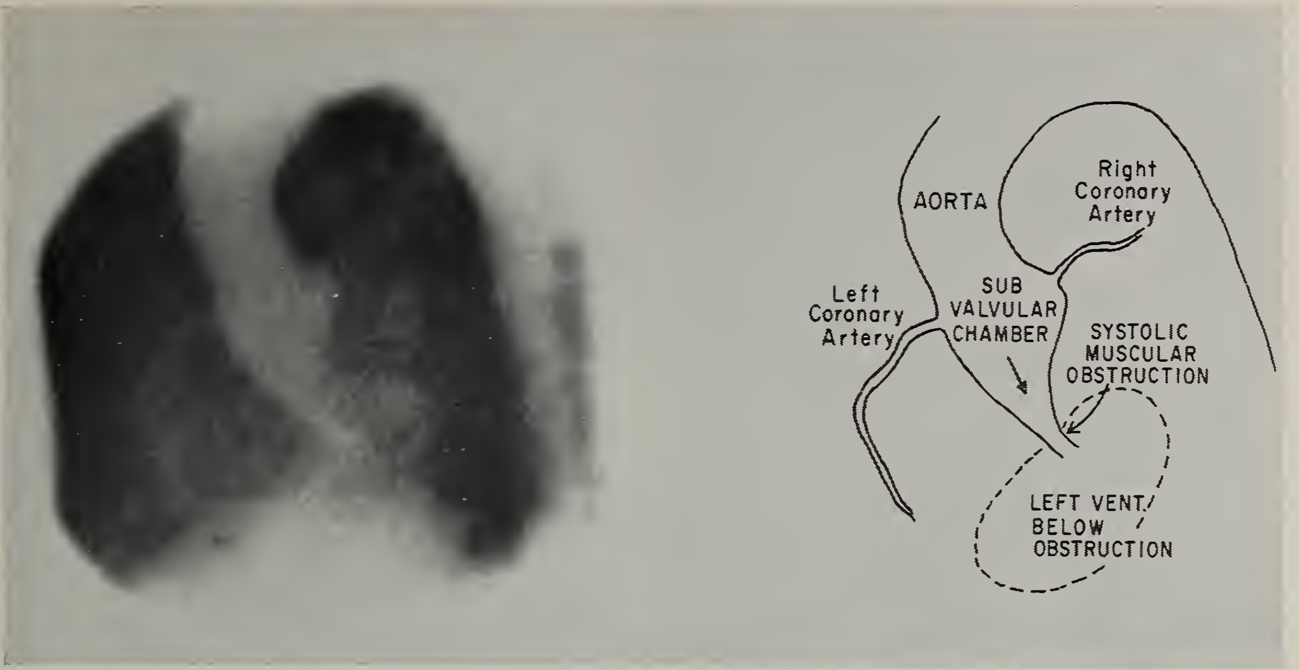

Figure 5.—Left anterior oblique cineangiogram demonstrating muscular "collar" obstruction of the left ventricle during systolic contraction.

firmed the presence of a high intensity ejection murmur at the left sternal border (Figure 3).

Cardiac catheterization was performed two days after admission (Table 1). A left ventricular angiogram examination ruled out a ventricular septal defect. Repeated pull-back pressure tracings at rest from the left ventricle to the ascending aorta did not demonstrate a systolic gradient across the valvular or subvalvular areas. However, a 36 mm systolic gradient in the subvalvular area was recorded with use of a constant infusion of isoproterenol (Figure 4). A cineangiogram from the left ventricle demonstrated a thickened subaortic muscular obstruction during ventricular systole (Figure 5).

Limited physical activities are being permitted with the patient under close clinical observation. The probable need of surgical intervention has been discussed with his parents.

Discussion

The murmur of hypertrophic subaortic stenosis is characteristically systolic in time, ejection in character and maximal at the left sternal border or apex. When faint, it is easily confused with a non-organic murmur and when loud it may be

TABLE 2.—*Factors in Differential Diagnosis of Hypertrophic Subaortic Stenosis*

	Hypertrophic subaortic stenosis	*Small ventricular septal defect*	*Mitral insufficiency*	*Functional murmur*
Onset of murmur	Usually after two years of age	Infancy	Any age	Any age
Character of murmur	Systolic ejection	Holosystolic or systolic ejection	Holosystolic	Systolic ejection
History of hypertrophic subaortic stenosis in family	Frequent	Rare	Rare	Rare
Symptoms of fatigue, chest pain, syncope	In moderately advanced or severe stages only	None	Rare	None
Electrocardiogram	Left ventricular hypertrophy	Normal, occasional left ventricular hypertrophy	Normal, left atrial hypertrophy or left ventricular hypertrophy	Normal
Teleroentgenogram	Normal, or some degree of cardiomegaly	Normal	Normal, or varying degrees of cardiomegaly	Normal

mistaken for the murmur of a ventricular septal defect or mitral insufficiency. The features differentiating these conditions are listed in Table 2. The essential point of differentiation lies in the electrocardiogram. Evidence of left ventricular hypertrophy associated with a murmur of this type is highly suggestive of hypertrophic subaortic stenosis.

Specific diagnosis may require heart catheterization and selective angiocardiographic studies. It is important to recognize that since the obstruction is dependent upon the contractile state of the ventricle, it may become evident only when the force of contraction is exaggerated by exercise, extrasystoles or administration of isoproterenol.[2,3] Extrasystoles in the normal heart or with fixed aortic stenosis are followed by an augmented ventricular contraction which is reflected by increased pressure in the left ventricle and the aorta. In this condition, there is increased obstruction during systole and the increased left ventricular pressure therefore may not be transmitted to the aorta.[8] When present this is a helpful diagnostic sign. Isoproterenol increases left ventricular contractility (inotropic effect) and accelerates cardiac rate (chronotropic effect). In the case reported here, 200 micrograms of isoproterenol were diluted in 250 ml of normal saline solution and infused at a rate of 80 drops a minute. As the heart rate increased from 80 to 160 per minute, a significant gradient was demonstrated in the subvalvular area.

Clinical symptoms of the disease are rare during childhood. Although the course of the disease is unpredictable, progressive obstruction of left ventricular outflow develops in many patients, with eventual left ventricular strain and lowered cardiac output. In such cases, dyspnea, chest pain, syncope and sudden death may occur.[4]

The condition is amenable to surgical correction; however, indications for operation have not yet been clearly defined. It is generally agreed that operative intervention should be considered in patients with progressive disease or with evidence of severe obstruction.

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Transtracheal Resuscitation

An Experimental Study in Dogs

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H. EARL GORDON, M.D., *Los Angeles*

■ *Previous experimental studies of the use of a large bore needle for transtracheal resuscitation have shown that arterial oxygen saturation can be maintained at satisfactory levels. Accumulation of carbon dioxide and subsequent fall of arterial pH has been the limiting factor in this mode of resuscitation.*

The present study was undertaken to demonstrate experimentally in dogs the use of an Intracath® 14 gauge needle for transtracheal resuscitation. Oxygen was administered transtracheally to five anesthetized apneic dogs for 30 minutes through this needle by the Bird respirator. Carbon dioxide could not be adequately exchanged by this method, but satisfactory levels of arterial oxygenation were maintained and all the experimental animals survived.

IDEALLY ALL PHYSICIANS should be trained to perform tracheotomy but it is probable that not many have had much experience with this procedure. In acute respiratory obstruction, such as may occur, for example, in epiglotitis or laryngotracheobronchitis, time may be of the essence. A mode of resuscitation should be available which can be easily utilized. Transtracheal resuscitation might serve this function.

Concepts of transtracheal resuscitation date from the 17th Century when Robert Hooke,[4] before the Royal Society of London, pumped air into the lungs of dogs and maintained life for well over an hour without respiratory movement. In 1944, Draper and coworkers[1] reported on experiments with diffusion respiration in which pure oxygen at one atmosphere was allowed to diffuse into the lungs of dogs while the animals were maintained in complete respiratory arrest for periods of 45 minutes. Jacoby and coworkers[6] in 1951 reported on transtracheal artificial respiration with oxygen insufflation through a 13 gauge transtracheal needle. They were able to maintain life in dogs for 30 minutes with an expected recovery rate of 100 per cent. Reed and coworkers[7] repeated this study in 1954 and noted a fall in arterial pH and a rise in arterial oxygen content and carbon dioxide tension. After 30 minutes of transtracheal respirations through a 13 gauge needle, they introduced a larger tapered needle transtracheally and carried out ventilation for an additional 30 minutes. All blood values and vital

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signs returned to normal. Postmortem studies revealed no evidence of hemorrhage or injury to tissues of the neck, trachea or lungs.

In 1956, Jacoby and coworkers[5] induced apnea immediately before operation in patients with malignant disease of the upper respiratory tract. An 18 gauge needle was inserted transtracheally and oxygen was administered at four liters per minute. Reversal in the progress of anoxia was noted within 30 seconds and oxygen saturation returned to normal within two minutes. These patients were artificially ventilated for periods of from five to 52 minutes.

In transtracheal resuscitation, a large bore needle is placed through the soft tissues of the neck into the trachea either through the cricothyroid membrane, the most constant landmark, or between the upper tracheal rings. Oxygen is administered through the needle at five to ten liters per minute. Life can be maintained without untoward effects for 30 minutes provided definite treatment is instituted within this period. The limiting factor is the build-up of carbon dioxide with resultant respiratory acidosis.

A majority of investigators[3,5,6,7] have recommended either a 13 or 14 gauge needle. Few hospitals have needles larger than 18 gauge readily available. In recent years, disposable non-surgical type cutdown sets such as the Bardic® Deseret Intracath® Unit* have been developed. The large size is supplied with a 14 gauge needle. These sets are being used in many hospitals and are usually available on each floor. Feder,[2] noting its accessibility, suggested the use of this needle for transtracheal resuscitation.

The present study was undertaken to demonstrate the use of the 14 gauge Intracath® needle in transtracheal resuscitation.

Method

Anesthesia was induced in five adult dogs ranging in weight from 9.5 to 28.6 Kg by intravenous administration of pentobarbital sodium. The femoral artery was cannulated with a polyethylene catheter, passed into the aorta and attached by means of three-way stopcock to a Statham strain gauge. Pressures and pulse rates were recorded on the direct writing recorder.

Specimens of blood were drawn from the femoral catheter at 10-minute intervals. Determinations of the arterial pH and carbon dioxide tension were performed with an Astrup ultramicro apparatus. Arterial oxygen saturations were determined with a Beckman Model DU spectrophotometer.

The animals were intubated with cuffed endotracheal tubes and maintained in the apneic state by the administration of pentobarbital and succinylcholine. Respirations were maintained by endotracheal administration of 100 per cent oxygen at pressures of plus 10 and minus 4 cm of water at 16 to 18 cycles per minute. After 30 minutes of assisted endotracheal respirations, the tubes were clamped and an Intracath® 14 gauge needle was inserted into the trachea through the thyrocricoid membrane or between the upper tracheal rings. By reversal of the plastic hub (Figure 2)

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*C. R. Bard, Inc., Murray Hill, N.J.

TABLE 1.—*Data on Five Adult Dogs in Which Ventilation Was Maintained by Transtracheal Insufflation*

Dog	*Weight Kilogram*	*Determination*	*Pulse*	*Blood Pressure mm of Mercury*	*pH*	*P CO_2 mm of Mercury*	*O_2 Saturation Per Cent*
1	28.6	Control*	150	210/130	7.38	21.0	92.0
		Transtracheal†	100	170/115	6.94	115.0	88.0
		Revival‡	150	160/125	7.29	31.0	92.0
2	17.7	Control	180	175/100	7.43	28.0	98.6
		Transtracheal	105	200/120	6.83	137.0	99.2
		Revival	165	165/80	7.25	36.5	99.1
3	22.2	Control	155	165/130	7.45	28.5	99.5
		Transtracheal	130	180/120	7.05	100.4	85.0
		Revival	150	170/145	7.44	32.0	100.0
4	21.2	Control	120	130/90	7.56	22.0	94.5
		Transtracheal	120	150/100	7.15	71.0	95.0
		Revival	160	130/96	7.38	35.5	100.0
5	9.5	Control	160	160/120	7.48	28.5	99.0
		Transtracheal	150	200/120	6.94	122.0	98.8

*Control—average of samples taken at 10 minute intervals during initial 30 minutes of endotracheal respiration.

†Transtracheal—results after 30 minutes of transtracheal oxygen insufflation.

‡Revival—results following ten minutes of assisted endotracheal respirations.

N.B.: Dog No. 5 was revived immediately following 30 minutes of transtracheal insufflation.

normally attached to the needle (Figure 1), a No. 6 Bird tracheal adapter (Figures 1 and 2) was attached to the hub, allowing for connection to the Bird respirator by interposition of an accordion connector (Figures 1 and 2). Transtracheal respirations were maintained for 30 minutes using 100 per cent oxygen at pressures of plus 30 and using 100 per cent oxygen at pressures of plus 30 and minus 5 cm of water, at 20 cycles per minute. The needles were then removed and the dogs were ventilated endotracheally for the final 10 minutes.

Results

Results are listed for each of the dogs in Table 1. Changes in the arterial pH and carbon dioxide tension began immediately after transtracheal respirations were begun. The pH fell from an average control level of 7.45 to 6.98 in 30 minutes. After resumption of endotracheal respirations for the final 10 minutes, the pH was 7.34.

Carbon dioxide tension rose from an average control level of 27.6 mm of mercury to 111 mm of mercury after 30 minutes of transtracheal insufflation. With the resumption of endotracheal respirations in the final 10 minutes, the level returned to an average of 33.7 mm of mercury.

No significant changes were noted in the oxygen saturation during transtracheal oxygenation nor were consistent changes seen in the arterial pressures. A slight decrease in pulse rate was recorded but returned to control levels during the final 10 minutes. All the experimental animals were easily revived.

Discussion

The data confirms previous work[3,5,6,7] demonstrating that dogs anesthetized to a state of complete respiratory arrest can be adequately maintained for 30 minutes by intermittent insufflation of oxygen through a transtracheal needle and then revived without ill effect. A large size Intracath® needle was successfully utilized for transtracheal resuscitation.

Slight motion of the diaphragm was noted during transtracheal insufflation with the Bird respirator. This motion was insufficient to produce adequate respiratory exchange. Excess carbon dioxide could not be removed in adequate amounts during the negative phase of the cycle. The carbon dioxide build-up cannot be reversed because of the small bore of the needle in relation to tracheal diameter.

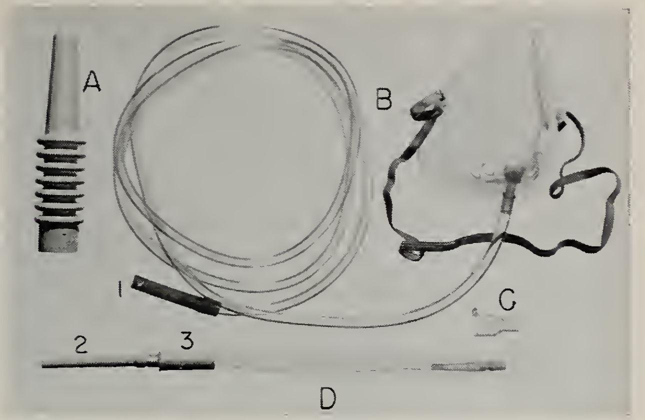

Figure 1.—Apparatus: A, Bird accordion connector, standard on machine; B, Standard disposable oxygen mask; 1, Rubber connector to oxygen source; C, No. 6 tracheal adapter for accordion connector; D. Bardic, Deseret Intracath® Unit, large; 2, 14 gauge needle in sheath; 3, Plastic hub.

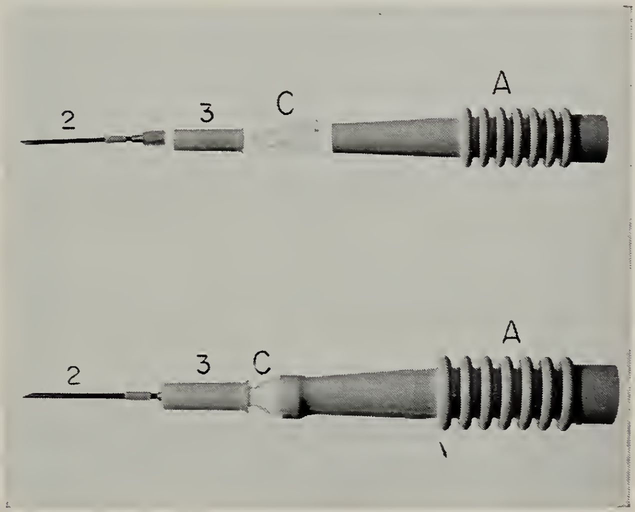

Figure 2.—*Above*, apparatus as used in experiment, unassembled; 2, No. 14 needle; 3, Hub reversed; C, No. 6 tracheal adapter for Bird; A, Bird accordion connector. *Below*, apparatus assembled as used in experiment.

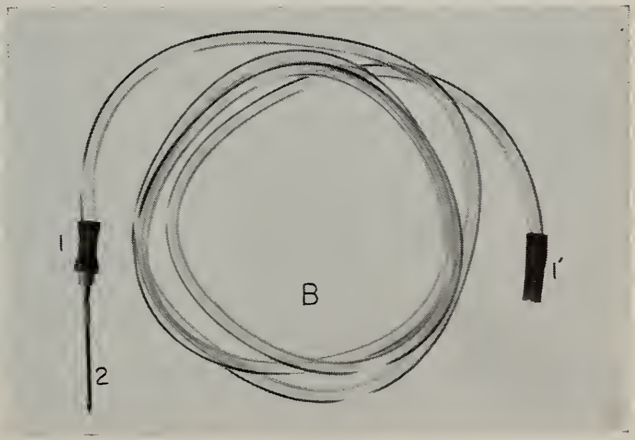

Figure 3.—Apparatus suggested in cases of emergency when Bird unavailable; 2, Intracath® 14 gauge needle; 1 and 1′, rubber connector (as shown in Figure 1) cut into two equal parts, each connected to ends of tubing, after removal of mask. 1 connects to oxygen source, 1′ to No. 14 needle.

As an alternate method, the Intracath® needle may be used transtracheally without attachment to the Bird respirator. The needle, without hub or catheter, is inserted into the trachea through the thyrocricoid membrane or upper tracheal cartilaginous interspaces. All that is required is an oxygen source and tubing. A standard disposable type oxygen mask (Figure 1, B) which in most hospitals accompanies an oxygen tank or is placed near an oxygen wall outlet, is quite suitable. The mask is removed and the polyethylene tubing is connected to the oxygen source by cutting the rubber connector (Figure 1, 1) into two equal parts and placing one-half at each end of the tubing (Figure 3, 1 and 1′). One end is connected to the 14 gauge Intracath® needle, the other to the oxygen source. Oxygen is then administered at 8 to 10 liters per minute.

Complications do occur with transtracheal resuscitation but are not usually of a serious nature.[7] The complications may include gastric dilatation from placement of the needle into the esophagus, subcutaneous emphysema, mediastinal emphysema, mediastinitis, hematoma and local abscess. The plug of soft tissue cored out by the needle during insertion could conceivably cause segmental atelectasis when blown into the lungs by the oxygen pressure.

In dealing with children, airway obstruction can be a challenging problem. Intubation and or tracheotomy may be quite difficult. The airway can be maintained in the pediatric emergency by the transtracheal technique.

This mode of resuscitation is suggested for emergency use only, and can only be employed in a hospital where oxygen is available. It is not meant as a substitute for orderly tracheotomy, but as a useful adjunct in resuscitation when tracheotomy cannot be readily performed. This technique should be used for as short a period as possible.

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Skin Cancer

Treatment by Curettage and Desiccation

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■ *Treatment of 104 skin cancers (75 basal cell carcinomas and 29 squamous cell carcinomas) by curettage and desiccation resulted in a 96 per cent five-year cure rate. Similar cure rates have been reported by other investigators. Cure rates less than 95 per cent may be attributable to insufficient skill or to the type of technique. Best results are associated with carrying out both the curettage and the desiccation twice for each lesion.*

ALTHOUGH CURETTAGE and desiccation of cutaneous neoplasms is widely used among dermatologists, sometimes physicians not experienced with the procedure question the advisability of treating skin cancer by this method. The following is a report of 104 skin cancers treated by curettage and desiccation with a minimum period of five years of follow-up.

Method and Material

This study comprised 90 patients with 104 skin cancers seen at the Dermatology Clinic of the University of California School of Medicine, San Francisco, during the years 1952 to 1958. Of the 104 lesions 75 were basal cell carcinoma and 29 were squamous cell carcinoma. A histologic diagnosis was obtained on all tumors. After treatment each patient was followed a minimum of five years (average 6.8 years) by the Visible Tumor Clinic.* The average age of the patients was 69 with a range of 27 to 85 years.

Results

The five-year cure rate for basal cell carcinoma was 96 per cent. The five-year cure rate for squamous cell carcinoma was 96.6 per cent. Metastasis did not occur in any case. The four recurrences were noted early and readily retreated.

Discussion

The 96 per cent five-year cure rate for treatment by curettage and desiccation compares favorably with the 95 per cent rate usually cited for treatment of basal cell carcinomas by surgical excision or radiation.[1,3] Also, the results are similar to those reported by others who used curettage and desiccation and maintained the patients under observation a minimum of five years.

Knox and coworkers[2] reported a 96.6 per cent five-year cure rate for 90 basal cell and squamous cell carcinomas. Ferrara[1] reported a 94.9 per cent rate for 82 skin carcinomas. These three studies indicate, then, that the same degree of cure rate can be obtained with curettage and desiccation of selected lesions as with excision or radiation.

Each of the three methods—curettage and desiccation, excision, and radiation—has its own advantages. Since many patients seek therapy for

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Submitted September 25, 1964.

*The University of California San Francisco Medical Center maintains a Visible Tumor Clinic in conjunction with the Visible Tumor Board which combines the experience of the various specialties involved in treating visible tumors. The services of this Board are available to all physicians for the diagnosis or treatment of neoplasms of skin or mucous membranes.

small early lesions, curettage and desiccation is frequently the treatment of choice. The advantages lie in the simplicity of the method. The entire procedure is accomplished in a single office visit without the need to occupy a hospital operating room, to use sutures or to have the patient return for multiple treatment sessions as in radiation therapy.

Although curettage and desiccation treatment of skin cancer is readily accomplished as an office procedure, only physicians well trained in its use and its limitations should use the technique.

Differences in individual physician's technique can lead to cure rates inferior to those of surgical excision or radiation. For example, Sweet and coworkers[4] reported an 88 per cent five-year cure rate, Williamson and Jackson[5] obtained a 93 per cent cure rate for 287 basal cell carcinomas with two physicians obtaining less than a 90 per cent cure rate. In the series reported by Knox and coworkers,[4] several physicians had treated patients in the study group, yet all recurrences were in patients treated by one. This points up the need for each physician to have careful training to achieve the desired 95 per cent or better cure rate.

Not only must differences in skill be considered, but also the type of technique. The relatively poor results reported by Sweet (88 per cent five-year cure) were associated with curettement of the skin cancer followed by a single desiccation. All the recurrences in Knox's group also were following the use of a single desiccation, in contrast to the double technique used by all other physicians in the study.

The technique advised by Knox and coworkers and favored by the author is as follows:

After local anesthesia is obtained, the skin cancer is thoroughly curetted with a 5 mm or larger curette until the physician can feel no tumor remaining. The curetted area plus an additional 2 to 4 mm border of normal skin is thoroughly desiccated. The curettage is then repeated using a smaller curette, say 2 mm, and a second desiccation is carried out, again including a 2 to 4 mm border of normal skin. The use of the smaller curette for the second curettage allows the physician to find additional tumor missed on the first curettement. These missed areas can be felt as tiny extensions of soft, epithelial tumor tissue compared with the firmness of normal collagen.

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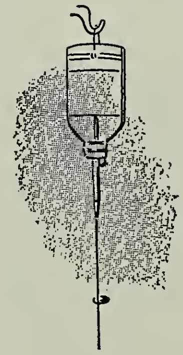

MONILIASIS

The Use of Candicidin Vaginal Ointment for Treatment

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■ *Candicidin vaginal ointment, 0.14 mg per gm of petrolatum base, was used in the treatment of 25 patients with monilial vaginitis. Ten of these patients were pregnant. All 15 of the non-gravid patients were cured, as proved by repeated cultures, after a maximum of three weeks of therapy. Eight of the 10 gravid patients were cured. Of the two patients with resistant cases, one had severe diabetes and the other had endocervicitis. Of 50 patients treated by insertion of Candeptin vaginal tablets, 42 became free of vaginal moniliasis after one or two 14-day courses of home treatment. All 42 remained free of infection for one month following treatment, as proven by culture. There were no instances of sensitivity to the preparation.*

VAGINAL MONILIASIS continues to be one of the most frustrating and disagreeable problems faced by gynecologists. Especially is this true when the patient has reached the end of her ability to endure the agonizing pruritus and her confidence in her physician diminishes.

Throughout the past 28 years, reports of so called cures have ranged from a few per cent of those treated to as high as 85 per cent.[5,7-10,15] However, recurrence has been quite ordinary,[2,3,5,10] probably often due to recrudescence rather than to infection anew.

The culture which produces candicidin was isolated during the summer of 1948 at Rutgers University Institute of Microbiology.[12,16] Candicidin is a potent antibiotic derived from a soil actinomycete similar to *Streptomyces griseus*. It is strongly antifungal and has shown promising results in the treatment of monilial infections. In fact, it is believed to be the most potent of the new group of antifungal antibiotics.[11,14]

Materials and Methods

We used two forms of dosage, a vaginal ointment and a vaginal tablet, in an investigation of the efficacy of candicidin against moniliasis. Candicidin vaginal ointment* was supplied in tubes, with plastic applicators. The vaginal ointment contained 0.14 mg of candicidin potency per gm of U.S.P. petrolatum base. Five cubic centimeters of the ointment was used intravaginally twice daily for two weeks.

Three milligrams of antibiotic dispersed in a starch-lactose base were contained in each one gram Candeptin® (candicidin) vaginal tablet.† The patient was instructed to insert one tablet high in the vagina in the morning and another at night for 14 days. Patients with severe vulvitis were permitted to use Candeptin ointment externally as needed in conjunction with the tablets. The patient was advised to avoid sexual intercourse during the 14-day treatment schedule. Cul-

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*Candicidin Vaginal Ointment (CS 2-VO) supplied by Julius Schmid, Inc., New York, N.Y.

†Candeptin Vaginal Tablets commercially available from Julius Schmid, Inc., New York, N.Y.

tures were taken one and four weeks following treatment.

The group receiving candicidin ointment consisted of 25 patients, 15 non-gravid and 10 gravid. One of each type was diabetic. The group receiving tablets included 50 patients, 28 non-gravid and 22 gravid. Follow-ups were made on all 75 patients with culture techniques.

All patients were from our own private practice and had similar backgrounds. Most had been under our care for other problems in the past and all were cooperative. In all cases diagnosis was established by use of smears diluted with 10 per cent sodium hydroxide and identification of the fungi under a microscope.

In each of the cases, cultures were made on Nickerson's media. At the end of two weeks, each patient discontinued the use of the preparation she was taking. Three days later a specimen of vaginal exudate was taken for culture. The patient was instructed not to douche or apply any intravaginal medication for 72 hours before the specimen was taken. If cultures were still positive the patient was instructed to renew the treatment schedule for another seven days and then to return for culture of a specimen again.

All patients having negative cultures after completion of treatment were requested to return four weeks later for a confirmatory culture. A third culture was made four weeks after the second negative culture. The patient was listed as "cured" only if three successive cultures were negative. Patients were requested to notify us immediately should any irritation become apparent.

Results

Of the 25 patients using candicidin vaginal ointment, 19 had negative cultures after one two-week course and no positive cultures thereafter. Another four patients had negative cultures after another week of treatment (Table 1). Thus, 92 per cent (all of the non-gravid and 80 per cent of the gravid patients) had negative cultures and no further positive cultures after a maximum of three weeks' treatment.

All the patients who had to have a second course of treatment for one week had cervical erosion or lacerations. Two of the patients who needed additional treatment, one gravid and one non-gravid, were diabetic. The two patients who still had positive cultures after three weeks of treatment were gravid. One of them had severe diabetes and the other had endocervicitis. Two of the patients had edema of the vulva, very mild in one case, following use of the medication. We assumed this reaction was due to a specific sensitivity. Any pruritus vulvae originally noted was relieved within a day or so in almost all patients.

TABLE 1.—*Results of Treatment of Moniliasis in 25 Patients with Candicidin Ointment*

Patients	*No.*	*Cured After One 14-Day Course*	*Cured After Additional 7-Day Course*
Non-Gravid	15	13 (87%)	15 (100%)
Gravid	10	6 (60%)	8 (80%)
	25	19 (76%)	23 (92%)

TABLE 2.—*Results of Treatment of Moniliasis in 50 Patients with Vaginal Candicidin Tablets*

Patients	*No.*	*Cured After One 14-Day Course*	*Cured After Additional 7-Day Course*
Non-Gravid	28	25 (89%)	27 (96%)
Gravid	22	13 (60%)	15 (68%)
	50	38 (79%)	42 (84%)

As to the 50 patients for which the simple but rather strict regimen with Candeptin vaginal tablets was prescribed, 25 of 28 non-gravid and 13 of 22 gravid patients became rapidly free of symptoms and remained free of symptoms and of positive laboratory findings for at least one month following cessation of treatment (Table 2). Although no further cultures were taken, all but two of these patients were seen again a month later and had no symptoms of vaginitis. The two that did not return were symptom free when they moved away. No instances of thrush were found in any of the newborn infants delivered of these mothers.

Discussion

We look upon the results in the non-gravid patients as unusually good. Although it is advisable to avoid intercourse during the treatment schedule to reduce the incidence of reinfection, it is not always possible to obtain patient cooperation. This may account for the poor results obtained with the gravid patients. In these cases the use of a condom is highly recommended, special emphasis being placed on the gravid patient, where laxity in this practice is most frequently noted. A number of other clinical investigators, working with the same or higher concentrations of candicidin in the vaginal ointment, reported similar or higher cure rates.[1,4,6,13,17] While our data show culture-proved cure rates of 92 per cent overall, or 80 per cent and 100 per cent in gravid and non-gravid patients respectively, other investigators, who perhaps are dealing with a more resistant infection, have suggested that somewhat higher dosages are required. We may also state that none of the other investigators have reported any irritation or side effects with this antibiotic. Candeptin vaginal ointment containing 0.6 mg of candicidin per gm of U.S.P. petrolatum (at least four times the dose used in this study) is now commercially available.

To date, use of candicidin vaginal ointment appears to be the most effective therapy for monilial vaginitis.

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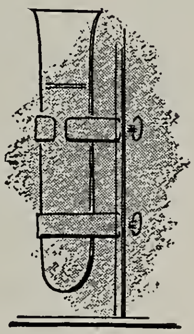

Methyl Bromide Poisoning

A Bizarre Neurological Disorder

RAYMOND P. COLLINS, M.D., *San Francisco*

■ *Methyl bromide, a widely used fumigant, may cause burns of the skin, fatalities accompanied by coma and convulsions, or prolonged neurologic and psychiatric symptoms. Burns are more likely to occur where evaporation is prevented under protective clothing. Symptoms of serious illness may not develop for hours after exposure. Since action appears to be one of methylation, especially of SH groups, B.A.L. may be helpful if used promptly.*

METHYL BROMIDE is a widely used fumigating agent, and sporadic outbreaks of serious human poisoning with it have occurred. In addition to the need to be aware of its toxic properties, unusual aspects of the hazards, toxic symptoms and mechanism of action of the drug make it an extraordinarily interesting one.

The following case is presented because of the diagnostic problem involved.

Report of a Case

A 22-year-old married white man was examined in September 1963, because of muscular difficulty of three weeks' duration. While on the bay fishing three weeks previously he had first noted numbness and awkwardness of his fingers whch made it difficult for him to tie hooks onto his line. This condition progressed so that in buttoning his clothes he could do only two to three buttons before fatigue made the task impossible. Clumsiness was more prominent in the right (dominant) hand. Weakness of leg muscles prevented his walking more than two blocks. There was no difficulty in chewing or swallowing and no impairment of vision.

The patient had previously been perfectly healthy and there was no familial history of neurologic disorder. He had, however, been working for a year and a half as a fumigator, mainly on the waterfront. The principal agent used was methyl bromide, delivered by a closed system under polyethylene tarpaulins sealed to the floor with sand snakes. The only known exposure, considered minimal by the patient, was on removing the polyethylene cover. A few days before the onset of symptoms he had used heavy concentrations of methoxychlor and dichloro - diphenyl - trichloroethane (DDT) when the Kafra beetle was discovered on a ship.

His height was 5 feet 6½ inches and his weight 131 pounds. Blood pressure was 120/70 mm of mercury. The liver was not enlarged or tender. Romberg's sign was present. The patient walked with a somewhat staggering, wide-based gait. Postural sense was depressed in the fingers and toes.

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There was mild weakness of the muscles of the hands and feet and a sensory level at the wrists and ankles. Vibration sense was diminished at the ankles. Supernator and ankle reflexes were absent. Toe responses were normal. Finger to nose approximation with eyes closed was mildly impaired due to loss of position sense, but there was no tremor. The hemoglobin was 14.8 gm per 100 ml of blood. A serologic test was negative for syphilis. Serum bromide level was non-detectable. An administered dose of radioactive B-12 was 9.7 per cent excreted in 24 hours (normal above 10 per cent). No abnormalities were noted in the spinal fluid and the protein content of it was 42 mg per 100 ml.

At this point peripheral neuritis due to DDT was suspected. The patient was allowed to continue the use of methyl bromide but not DDT or other chlorinated insecticides. But by January 1964, there was increased weakness of the legs and loss of balance. The patient had fallen off a ladder.

Now patellar and biceps reflexes were absent as well as the Achilles and supernator reflexes. Toe responses were abnormal. Vibration sense was absent at ankles and knees, weak at the pelvis, normal on the sternum. Touch, thermal and pain sense were diminished in the legs. Motor power was grossly reduced in the hands. The gait was abnormal because of anterior tibial weakness, impaired position sense and ilio psoas weakness which made it difficult for the patient to stand at all. Results of cerebellar and cerebral lobe tests were normal. He was alert and well oriented.

Hemoglobin was 15.8 gm per 100 ml. Leukocytes numbered 11,800 per cu mm. Urinalysis was within normal limits and there was no albumin present. The sedimentation rate (Wintrobe) was 8 mm in one hour. An electrocardiogram was within normal limits. Fasting blood sugar was 74 mg per 100 ml. Serum bromide ranged from 3.0 to 10.0 mg per 100 ml on several determinations. A fat biopsy showed no abnormal elevation of the content of DDT, methoxychlor or chlordane. Blood urea nitrogen was 17.2 mg per 100 ml. Alkaline phosphatase was 6 King-Armstrong units.

The patient was removed from his work and exposure to methyl bromide. Recovery was progressive. By June 1964, he could run short distances and walk six blocks. Reflexes had returned but the ankle reflex was sluggish. There was still some hypesthesia of the legs. Motor power in the hands was greatly improved. Vibration sense was still absent at the ankles but present at the knees. By October 1964, there was only slight weakness of muscles, coordination was normal and the patient was working.

Uses, Intoxication, Treatment

Methyl bromide is a gas at room temperature. The liquid boils at 4.5°C, yielding a gas which is three times as heavy as air. It has a musty, acrid odor in high concentration. Although odorless at lower concentrations, it is still highly toxic. Its high penetrating power and freedom from fire or explosion hazard enhance its value as a fumigating agent. Fire extinguishers make use of the heaviness of methyl bromide vapor to smother a fire. This use and that of refrigerant have been abandoned because of toxicity. Heated in the presence of air, methyl bromide decomposes to yield hydrogen bromide, bromine, carbon monoxide and carbonoxy bromide.[26] These decomposition products have occasionally persisted in a house fumigated while a pilot light was left burning and caused irritation of the eyes, nose and throat.[17]

Today the major use of methyl bromide is as a fumigating agent and it is this use that produces most of the poisonings. In one type of operation a fixed air-tight fumigation chamber is utilized. Although poisoning has resulted from leakage through walls that were not air-tight or from entering a room too soon after fumigation[8,10] these installations are now generally well engineered with adequate exhaust fans. The more hazardous operation is that done on the spot—on the dock, in the ship or at a warehouse. Polyethylene sheeting is placed over the goods or structure and sealed down with sand-filled "snakes." Methyl bromide is fed through tubing under the sheet. The hazard comes 24 hours later in removing the sheeting or airing out the building. Exposure may come from faulty sealing, from residual methyl bromide on the tarpaulin handled and placed into the work truck, from residual gas trapped in and around the product fumigated, from exposure to air under the tarpaulin or from faulty gas masks.[21]

Toxic exposure may affect the skin, lung, kidney and liver, but is especially noted for producing neurologic and psychiatric manifestations. Inhalation is the usual route for systemic poisoning but gastrointestinal absorption is a possibility. Systemic poisoning, even fatalities, have occurred from absorption through the skin alone.[11] Exposure to 10,000 parts per million (ppm) for a few minutes is fatal, with death due to pulmonary edema. At this level odor and mucous membrane irritation serve as a warning. Symptoms have occurred at levels of 35 ppm, the lowest level at which the halide flame will detect the presence of the gas. The ceiling value for permitted exposure is given as 20 ppm.[25]

The most notable features of methyl bromide toxicity are the latent period of two to forty-eight hours after exposure before onset of symptoms, and the possibility of experiencing a fatal exposure without any awareness of exposure at all. Clarke, Roworth and Holling[5] described dramatically such an occurrence in the British Navy. A leaking methyl bromide fire extinguishing system exposed four officers while they were eating lunch in the wardroom. All four became ill and two died. The two officers exposed the longest noted smarting of the eyes, but did not become seriously ill until four hours later, when both vomited and one became unconscious. After they were admitted to hospital, a hearing officer was sent to hold an inquiry into the cause of this illness. The third of the four officers summoned to the hearing, which was held in the same wardroom, was perverse, uncooperative, and unconcerned at his fellow officers' serious plight. The hearing ended with some suspicion that the steward had poisoned the two officers, since he was under punishment and had discarded the remains of the meal. It was only later, when the hearing officer noted smarting of his own eyes, that the atmosphere in the wardroom and the fire extinguishing system was suspected.

Following exposure, irritation of eyes and mucous membranes may be noticeable. Within a few hours malaise, headache and nausea develop. With the mildest exposures this may be all. After two to sixteen hours the more serious symptoms develop, including visual disturbance, speech disturbance, irrational behavior, drunkenness and drowsiness. During 1945 in California when some 200 employees of the date packing industry were ill with methyl bromide poisoning, two men were jailed as marijuana addicts before it was realized their violent behavior was due to methyl bromide.[8] A latent period of 15 days has been reported before the onset of fainting attacks, manic symptoms and tremor persisting at least four months.[23] Tremor may progress to myoclonic jerks and convulsions. Fatal cases have been characterized by coma and frequent convulsions, difficult to control. Death occurs in 24 to 48 hours with circulatory failure or pulmonary edema. If the patient survives such a serious exposure, or has had repeated exposure to lower concentrations, neurologic and psychiatric abnormalities may persist for months or years. Visual disturbances such as double vision, inability to read and difficulty focusing occurred in all of Johnstone's 34 cases.[10] Other symptoms have been visual and auditory hallucinations,[21] staggering, stammering,[4,30] illegible handwriting,[23] mydriasis,[7] cogwheel rigidity, depression, apathy and pathological reflexes. Ataxia and epilepsy have persisted two years.[21] Spastic paresis lasted one year.[11] Intention tremor, cogwheel rigidity and increased reflexes have lasted ten months.[21] Carter[4] reported one patient and DeJong[5a] three patients with neurologic manifestations very similar to those observed in the present case.

Methyl bromide is a vesicant like mustard gas, but only when evaporation is prevented.[6] It can penetrate clothing, shoes and even rubber boots. Burns are more likely to occur in the seemingly more protected areas of the body in preference to open skin—under face masks,[21] under shoes[1,3] and under trousers of men bare to the waist.[11] One man splashed methyl bromide on his face with no serious consequences but blisters containing one-half pint of fluid developed on his feet which had been protected with waterproof boots.[24] Hence the remarkable recommendation that protective gloves not be used.[3] The skin changes show the same latent period, with burning sensation developing in an hour and erythema and blisters in several hours.[1,11] A papular rash has developed as much as seven to nine days later.[1,5]

Although clinical renal failure appears not to be common, Benatt and Courtney[1] reported on a patient with vomiting, hiccoughs, apathy and scanty urine. The blood urea nitrogen reached 345 mg per 100 ml on the eighth day and was still 80 mg eight months later.

Laboratory studies are of little value in the evaluation of the patient. Blood bromide levels are far lower than those of inorganic bromide poisoning, ranging from 1.0 mg to 40 mg per 100 ml. Symptoms have been present at 2.8 mg per 100 ml[21] and fatalities at 8 to 9 mg,[5] but detectable levels persist for a month.[23] Albuminuria, red cells and casts have been present in the urine.[1,14,20] The serum alkaline phosphatase has been elevated.[20]

Autopsy reports describe congested and edematous lung,[5,19] degeneration and necrosis of renal tubules[5,20] central lobular necrosis of the liver[19] or cloudy swelling and fatty change,[5,7] hemorrhagic gastroduodenitis,[7] hyperemia of the meninges and edema of the brain[14,20,26] and hemorrhages and degeneration of ganglion cells in the brain.[5,11,14,23,26]

The mechanism of action of methyl bromide is a fascinating subject. The obvious first assumption is that toxicity must be related to the bromide portion of the molecule, but serum bromide levels never reach the levels significant of inorganic bromide poisoning. Methyl alcohol, also produced by the hydrolysis of methyl bromide, might contribute to the symptoms, but the optic atrophy of methanol poisoning is never seen in methyl bromide poisoning and neither methanol nor inorganic bromide causes repetitive convulsions. Furthermore, Smith and von Oettingen[22] did not find methanol in the blood nor increased formic acid in the urine of dogs poisoned with methyl bromide. Irish, Adams, Spencer and Rowe[9] failed to produce symptoms of methyl bromide poisoning in rats and rabbits that were exposed to methanol eight hours a day for six to nine months and were fed NaBr to a blood bromide level of 90 mg per 100 ml. Miller and Haggard[18] produced evidence that methyl bromide passes readily through the cell membrane, unlike inorganic bromide, and suggested that intracellular bromidism is produced. The solubility of methyl bromide in fat and its concentration in brain tissue has been offered as a factor in toxicity.[26]

None of these theories, however, explains the striking similarity between the toxicity of methyl bromide and methyl chloride. There is the same delay in the onset of symptoms[15,22] and the same convulsions.[12] Neurologic symptoms such as ataxia, foot drop and blurred vision have persisted a year with methyl chloride poisoning.[16]

Dixon and Needham[6] in a study of chemical warfare agents noted that methyl bromide acts like mustard gas on the skin, showing the same two-hour delay in development of erythema, and the same strong inhibition of hexokinase which catalyzes the phosphorylation of glucose to glucose-6-phosphate. Lewis[13] demonstrated that methyl bromide acts as a powerful methylating agent. S-methyl cysteine can be extracted from a protein solution treated with methyl bromide. Appearance of free bromide ion is quantitatively related to the methylation of SH groups of cysteine and glutathione. SH-containing enzymes such as urease, papain, succinic dehydrogenase and yeast hexokinase are irreversibly inhibited. Wintering-ham[27,28,29] showed that methyl bromide interferes with phosphorus transfers in energy metabolism, that triose phosphate dehydrogenase, an SH-containing enzyme, is inhibited, and suggested that the methylation of histidine might interfere with the metabolism of histamine and nerve function.

It seems probable, then, that one or a few important enzymes in the nervous system, such as hexokinase and pyruvate oxidase, are unusually susceptible to inactivation by methylation of SH groups to explain the sensitivity of the nervous system to small concentrations of methyl bromide and methyl chloride. Interference with the metabolism of pyruvate, where thiamine acts as a coenzyme, would explain the similarity to the neuropathic manifestations of thiamine deficiency. Since heavy metals also damage enzymes by attaching at sulfhydryl groups, it is not surprising that somewhat similar neuropathic and psychopathic changes occur in poisoning with mercury, arsenic and lead.

Since the major point of attack appears to be SH groups, B.A.L. (dimercaptopropanol) has been suggested for treatment. If given beforehand, B.A.L. protects against a lethal exposure in animals,[2,28] but has much less effect given after the exposure. B.A.L. was used in one clinical outbreak of poisoning with reason to believe that it was helpful.[21]

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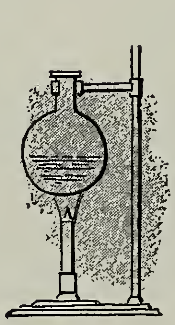

Corticosteroid Therapy In Childhood Asthma

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■ *Fortunately, nearly all cases of asthma in childhood can be managed successfully without the use of adrenal corticosteroids. However, when used properly the corticoids enable that small group of children who have not responded to traditional allergic management to lead normal lives. The action of these compounds is a pharmacologic and not a physiologic one. The adrenal corticosteroids suppress the symptoms of childhood asthma but in no way serve as curative agents of allergic disease.*

THE ADRENAL CORTICOSTEROIDS were introduced as pharmacological agents in clinical medicine 16 years ago.[36] These anti-inflammatory substances now are being used extensively in pediatrics in the management of blood dyscrasias,[52] childhood nephrosis,[9] connective tissue disorders[51] and traditional "allergic" diseases—asthma and atopic dermatitis.[53,56,61] This review is an assessment of the role of the corticosteroids in childhood asthma.

Steroids—Structural Relationships

Steroids are lipid substances which are distributed widely in nature. A large number of them are produced by the adrenal cortex but, of these, hydrocortisone (cortisol) is the chief natural compound with anti-inflammatory activity. Its structure and the configuration of some common synthetic agents which share the basic steroid molecular structure necessary for anti-inflammatory activity are shown in Figure 1. All anti-inflammatory steroids are members of the carbon-21 glucocorticoid series and have hyperglycemic, protein-wasting, ACTH-suppressing and eosinopenic effects. Hydrocortisone is transported in the circulation in the 17-hydroxycorticoid fraction loosely bound to plasma protein. Ninety per cent of it is reduced and conjugated in the liver with glucuronic acid and excreted in the urine by glomerular filtration.

The physiologic and pharmacologic effects of all these compounds are similar, with minor variations. The pharmacologic potency of any corticoid is dependent on the intensity of the end-organ response as well as the survival time of the corticoid in an active state in body fluids. The relative anti-inflammatory potencies of various steroid preparations are shown in Table 1.

Corticosteroid preparations can be administered via the oral, intramuscular, intravenous, rectal or inhalation route. With the administration of oral steroid medication, the peak blood concentration occurs in four to eight hours, with subsequent rapid decline. Absorption by the intramuscular route is variable, depending on the vehicle in

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TABLE 1.—*Relative Anti-Inflammatory Potencies, Showing Amount of Various Corticosteroid Preparations Needed to Have Effect Equal to 25 mg of Cortisone*

	Milligrams
Cortisone	25
Hydrocortisone	20
Prednisone	5
Prednisolone	5
Methyl prednisolone	4
Triamcinolone	4
Dexamethasone	0.75

which the drug is contained. Some intramuscular preparations are absorbed over a period of several weeks. Systemic absorption also occurs in varying degrees when the drugs are administered by inhalation.

In this review, the term *steroid* or *corticosteroid* will be used interchangeably with hydrocortisone, the naturally-occurring hormone of the adrenal cortex after which many synthetic anti-inflammatory agents have been patterned.

Asthma—Basic Concepts

Asthma, a reversible clinical syndrome, consists of cough and wheezing due to smooth muscle spasm, mucosal edema and excess mucus production in the bronchial tree. Many clinicians consider this disease to be episodic, but most children with asthma have underlying respiratory symptoms between attacks, particularly if the illness is not under good control. These "continuity symptoms" are coughing or wheezing with exertion and coughing at night. There are also usually associated symptoms of nasal allergic sensitivity—nasal itching, sneezing and rhinorrhea.[16]

Asthma in childhood is considered to be an allergic disorder. Allergy, a term first used early in this century by von Pirquet,[64] describes the "altered reactivity" of an organism upon reexposure to a foreign substance or allergen. Recently, Gell and Coombs[14] classified the allergic reactions into four categories (Types I to IV), depending upon the basic mechanisms that occur. The Type I reaction, characterized by the combination of antigen (allergen) with antibody which is already present on the cell surface, subsequently leads to the release of such mediators as histamine, which then produce a variety of pharmacologic effects. The Type II allergic reaction is characterized by the combination of antibody with the tissue cell, or antigen, or hapten which has been intimately associated with the cell (auto-immune hemolytic anemia). Type III reactions depend on antigen-antibody complexes in antigen excess (serum sickness), and Type IV reactions encompass the delayed hypersensitivity phenomena (tuberculin reaction).

Atopy is a term which was introduced by Coca in 1923[11] to describe the type of hypersensitivity which is peculiar to man, subject to hereditary influence, associated with circulating antibody (reagin) and manifesting such clinical syndromes as hay fever and asthma. Atopy encompasses one part of the broad field of allergy. Human atopic reactions are Type I allergic reactions and underlie most cases of childhood asthma. Atopic persons have the capacity to become sensitized to a number of different inhalant and food substances or allergens which are innocuous to more than 90 per cent of the general population. They also usually have family histories of atopic disorders and increased numbers of eosinophiles in nasal secretions and peripheral blood. It is theorized that, in atopic persons, the allergen enters the body via a natural route—respiratory tract, gastrointestinal tract or skin—and evokes the production of circulating reaginic antibody which also has skin sensitizing activity. This antibody becomes fixed to cells in the "shock organ"—nasal mucosa, bronchioles, skin. On subsequent exposure, the allergen reacts with the reaginic antibody on the cell surface, and a number of pharmacologic mediators are released (histamine, slow-reacting substance, bradykinin and probably others). Through their effects on blood vessels, mucosal glands and smooth muscle, these mediators produce an inflammatory response. Considerable basic investigation is being done on other immune phenomena in the allergic reaction which, presumably, underlie the mechanisms that operate in most cases of childhood asthma.[38]

The most common environmental allergens are house dust, animal danders, pollens and molds. In food allergy, which is less common, the immunologic mechanisms are more obscure since there is little correlation between the presence of specific reaginic antibody on skin testing and clinical symptoms. In both inhalant and food cases, one must distinguish between the underlying specific allergenic factors in asthma and a host of nonspecific "trigger" factors[16] such as chemical irritants, climatic changes, respiratory infections, emotional factors, autonomic reflex phenomena and probably many other unknown variables.

Most children with asthma respond to the traditional approach of removing as much of the offending allergen as possible, followed by injection therapy in selected cases. The remaining respiratory symptoms can usually be controlled with bronchodilators. Even though some of these children may have constant mild symptoms and periodic acute exacerbations, they are able to lead essentially normal lives. A few, however, continue to have difficulty in spite of good allergic management. Some continue to be extremely sensitive to usual allergens; others are not particularly reactive either clinically or on skin testing. Unrecognized food allergy may be present. Emotional factors are often quite prominent in this group, but it is usually difficult to determine whether they are of etiologic significance or represent a reaction of the child to chronic illness.

When chronic asthma becomes severe, the airway becomes extremely "irritable" and may react in an adverse way to a variety of stimuli which are ordinarily innocuous. At this point one is faced with a chronic and disabling illness which can have a tremendous impact on the child and his family. It is in this small group of children in whom traditional allergic management fails or is only partially successful, that steroid therapy deserves consideration.

Mechanism of Corticosteroid Action in Asthma

Theoretically, corticosteroids may interrupt the sequence of immunologic events which lead to the production of symptoms in asthma by three mechanisms: direct inhibition of tissue inflammation, antagonism of histamine or its precursors, or by suppression of antibody formation.

Direct Inhibition of Tissue Inflammation

The effects of hydrocortisone in tissue inflammation have been studied extensively. Experimentally, radioactive hydrocortisone has a half-life in the blood of about 45 minutes and exerts its anti-inflammatory effects in tissues within the first hour after injection. Apparently, the level of hydrocortisone necessary to inhibit inflammation is present in tissue for a shorter period than the duration of the anti-inflammatory effect; this may be due to the initiation of a response in the connective tissue fibroblast.[20] The corticosteroids inhibit capillary permeability, help to reduce transudation of fluid from the vascular tree and inhibit the synthesis of chondroitin sulfuric acid in connective tissue ground substance.[2]

The cells of the hemopoietic system are intimately involved in non-specific as well as allergic inflammatory responses and are affected in a variety of ways during therapy with steroid hormones. There is an increase in polymorphonuclear neutrophiles in the circulation. Their survival time is increased but their ability to phagotize cells and their ameboid activity is diminished. While the role of the eosinophile in inflammation is not clear, it is well known that steroids depress the circulating levels of these cells. Lymphocytes are intimately involved in delayed hypersensitivity reactions (Gell and Coombs Type IV) and are depressed in the blood and tissues during corticoid therapy. The action of the corticosteroid hormones on tissue inflammation appears to be the major factor in relief of clinical symptoms in asthma.

Antagonism of Histamine or Its Precursors

Corticosteroids have little effect on the release of histamine; they do not inhibit the rapid pharmacologic action once it is present in the circulation, and they are not beneficial in the immediate treatment of the human anaphylactic reaction. Goth,[30] however, has shown that they do prevent the reaccumulation of histamine in tissues after previous discharge. Mast cells, possibly a major source of histamine in the allergic reaction, are altered by hydrocortisone—they diminish in number, become vacuolated and acquire irregular outlines. The size of the granule changes, and the uptake of radioactivity labeled sulfate is inhibited.[2]

Schayer[49] recently proposed that there are two types of histamine which play a role in the inflammatory response—*extrinsic* histamine obtained from mast cells and released into the general circulation, and *intrinsic* histamine formed through the action of histidine decarboxylase in vascular endothelial cells at the precapillary arteriolar level. Intrinsic histamine exerts its effect locally, is not affected by systemic antihistamines and is under the regulation of the glucocorticoid hormones. Clinically, the response of most cases of asthma to antihistamines is discouraging and, unless one accepts Schayer's theory, the role of steroids on histamine metabolism is probably a subsidiary one.

Suppression of Antibody Formation

Since reaginic antibody (reagin) plays a role in human atopic disease, it is interesting to speculate about steroid suppression of antibody formation as a factor in diminishing the allergic reaction in asthma. Studies concerning this point have been performed in animals, using various antigen-antibody systems. In rabbits treated with corticoids, antibody production was inhibited during the primary response following antigenic stimulation. This effect, less pronounced but still present, followed secondary anamnestic stimuli.[22] Steroids apparently inhibit antibody synthesis and do not increase antibody catabolism, since antibody disappearance curves in passively sensitized cortisone-treated animals are similar to the curves for untreated controls.[22] The steroids, as mentioned, reduce the number of tissue lymphocytes and probably suppress antibody production through their effects on these cells.

General or local anaphylactic reactions depend upon the "fixation" of antibody by cells and subsequent release of chemical mediators following antigenic stimulation (Gell and Coombs Type I allergic reactions). The corticoids inhibit anaphylactic reactions in some species, such as the mouse, where vascular permeability factors, cellular aggregation and other mechanisms may be prominent. However, in the guinea pig and in man the effects of anaphylaxis are more dependent on the chemical mediators and are little influenced by steroids.[22] Adrenal cortical hormones do not protect passively sensitized guinea pigs from systemic anaphylaxis or local passive cutaneous anaphylaxis (PCA) which requires minute amounts of antibody.[46] In humans, the local anaphylactic reaction of the allergy skin test, which is dependent upon the presence of reaginic antibody, is also not affected by steroid therapy.[40]

Studies to date have shown partial inhibition, but never complete suppression, of antibody synthesis during corticoid treatment. With the dosages used currently in clinical situations, it is unlikely that this mechanism is very important in allergic reactions.[37]

Short-Term Therapy

Corticosteroids can be used effectively in the management of the acute asthmatic attack. Large doses, given over a period of seven to ten days and tapered rapidly or stopped abruptly may prevent hospitalization or shorten it. Many of the dangers of chronic steroid therapy can be avoided when the duration of treatment is less than three to four weeks; there is laboratory evidence of a normal adrenal pituitary axis response soon after cessation of therapy. However, it must be emphasized that the normal response to stress of the adrenal glands may be suppressed for several months afterward,[63] so that close follow-up during this time is mandatory.

Repeated short courses of steroids should not replace good allergic management, and vigorous attempts at control of acute episodes with bronchodilator medication should always be made. The treatment of severe status asthmaticus demands adequate hydration, expectorants, oxygen, bronchodilation—often, inhalation therapy to deliver moisture and medication to the bronchial tree; and, rarely, use of a bronchoscope for removal of secretions. Corticoids are of undoubted therapeutic benefit but should not be relied upon exclusively. Experimentally, they can cause cellular changes within one to two hours[20]; however, in a severe asthmatic attack clinical improvement does not usually occur that rapidly. With a comprehensive treatment regimen, it is often difficult to assess the role of hydrocortisone in the improvement of clinical symptoms.

Large doses of steroids given over a short period in conjunction with other therapeutic measures, can be of aid in distinguishing between a reversible and an irreversible pulmonary disease process. Tooley and Nadel[60] studied the pulmonary function in a group of ten children with severe asthma before and after a therapeutic regimen which included large doses of steroids for one to two weeks. They found evidence of severe obstructive airway disease in all patients before treatment. After therapy, all of them had normal pulmonary function. At present, childhood asthma appears to be a reversible process but pulmonary function studies of more patients over a longer period will be necessary to resolve this issue.

Continuous or Long-Term Steroid Therapy

The initial enthusiasm for the pharmacologic benefits of the adrenal corticoids was dampened considerably by the serious adverse side effects which may occur with long-term use.[29] These untoward effects must be weighed carefully when considering steroid therapy in any illness. In childhood asthma there are two great dangers in the use of these agents: adrenal insufficiency and growth suppression. The other common major hazards to steroid therapy are well defined, and some unusual complications have been described.

Adrenal Insufficiency

The effect of exogenous corticoids on the pituitary-adrenal axis is the major reason why these drugs must be used with great caution. Exogenous administration of hydrocortisone inhibits the secretion of ACTH by the pituitary gland resulting in diminished output of glucocorticoids and adrenal atrophy. The extent to which this occurs depends on the dosage of corticoid medication, the type and duration of treatment and unknown variables in the individual patient.[63] Thus, abrupt cessation of continuous steroid therapy or the development of sudden stress in a patient receiving corticoids may result in the classic symptoms of adrenal insufficiency—for example, irritability, headache, abdominal pain, vomiting, weakness, pallor, shock and death.[23]

Urine and serum hydroxycorticoid levels before and after ACTH stimulation provide laboratory evidence for adequate adrenal function. Ketogenic steroid levels following administration of methapyrapone (SU 4885) help to test the adequacy of pituitary ACTH function.[25,28] Wood,[66] however, pointed out that failure of the pituitary adrenal axis to respond to stress cannot be excluded by an ACTH stimulation test. Laboratory evidence of a normal pituitary-adrenal axis does not rule out the possibility of relative adrenal insufficiency in the event of a severely stressful situation.[63] There have been reports on the development of acute adrenal insufficiency at surgical operation that is done during or following cessation of steroid therapy.[24,47] The risks of long-term steroid treatment begin to occur when the duration of therapy exceeds three to four weeks.

Growth Suppression

Retardation of growth is shown by patients with Cushing's syndrome who have excess circulating 17-hydroxycorticoids.[59] The adrenal corticosteroids suppress linear growth through an inhibitory effect on epiphyseal cartilage which may be the result of antagonism with growth hormone.[4,35] Growth rates of children with severe allergic disease also may be diminished, but increase decidedly when allergic symptoms are ameliorated.[12] In 1956, Blodgett and coworkers[6] administered cortisone in dosages greater than 45 mg per square meter of body surface per day and produced a reduction in growth rates within several weeks. When the drug dosage was reduced below this critical level or was stopped entirely, a growth spurt with a return to normal levels ensued. Van Metre and coworkers[62] studied the comparative growth-inhibiting effects of a number of different steroid preparations in childhood asthma and found that prednisone and methyl prednisolone had growth suppressive effect at a dosage of 5 mg per square meter of body surface per day compared with 55 mg per square meter for cortisone. Since the difference is more than ten-fold and the anti-inflammatory activity of cortisone is one-fifth that of prednisone, cortisone appears to be the drug of choice for patients in whom growth suppression is apt to occur.

Obviously it would be helpful to have knowledge of the growth pattern of the child before beginning continuous steroid therapy, but it is most important to have frequent and careful height measurements of the child while he is receiving these drugs.

The more common complications of chronic steroid therapy are well known to most physicians:

- The typical cushinoid features of hyperadrenalism.[58]
- Osteoporosis, because of the anti-anabolic effect of hydrocortisone on protein metabolism leading to a deficiency of bone matrix, and because of impaired calcium absorption and increased losses of calcium and phosphorus in the urine and stool.[44] Osteoporosis is more commonly observed in middle-aged or older adults and in children with such diseases as rheumatoid arthritis, where immobilization is a prominent factor.[18] It is not usually a serious problem during steroid therapy in chronic asthma.
- Hypertension — blood pressure should be monitored regularly.[43]
- Electrolyte abnormalities—sodium retention and potassium loss—which are much less common since the advent of the newer steroid analogues.[42]
- Increased glyconeogenesis, which can lead to and increase in blood sugar, glycosuria and symptoms of diabetes.[13,19]
- Gastrointestinal bleeding which can result from the effect of the steroid hormones on acid secretion and mucosal resistance.[31]
- Altered personality patterns and frank psychotic episodes.[10,27] A patient's emotional status should be assessed before initiating long-term therapy.
- Susceptibility to infection is increased in certain patients who receive continuous steroid therapy.[26,45] These patients usually have severe dis-

ease processes which also alter host resistance (but this factor does not exist in asthma). Corticoids which suppress the local inflammatory response to infection may also alter the host's immune response to the infecting agent. For example, steroids can suppress the delayed hypersensitivity response to tuberculin and cause activation and spread of a latent tuberculous process.[45] Any child with asthma in whom long-term steroid therapy is contemplated should have a preliminary tuberculin test,[50] chest x-ray and periodic films of the chest during the course of therapy. The development of overwhelming bacterial lung infections in asthmatic children on prolonged steroid therapy is uncommon. The diagnosis of pneumonia is often difficult to make in an asthmatic patient since the rapidly changing infiltrates seen on the chest film are often due to atelectasis.[39] However, since steroids may suppress the systemic manifestations of infection, this diagnosis should be suspected in any asthmatic patient whose condition deteriorates while receiving them. Although overwhelming viral infections—particularly with childhood exanthemata—have been observed in many steroid-treated disease entities,[32] they are unusual in asthma.

- Other effects: pseudotumor cerebri; acute hemorrhagic pancreatitis[3]; myopathy, seen most frequently with triamcinolone, but also with other preparations[8,65]; posterior subcapsular cataracts (in patients with rheumatoid arthritis[5]); and peculiar skin lesions of panniculitis (following steroid withdrawal in patients with acute rheumatic fever[57]).

Since childhood asthma is a reversible disease with a very low mortality rate, the reasons for initiating continuous steroid therapy must be critically examined. The corticoids must not be started until every suspected underlying cause has been investigated thoroughly. It is difficult, if not impossible, to interpret the effects of a regimen for allergic disease while the patient is receiving steroids.

A few asthmatic children do not respond to good allergic management and have to have many admissions to hospital and numerous trips to the emergency room. They miss much time at school, have many sleepless nights, create a financial burden for the family and significant emotional stress for themselves and their parents. The point at which prolonged steroid therapy becomes justified depends on how the child and his family react to the illness. Some children can lead reasonably normal lives in the face of severe asthma; in others, a moderate amount of asthma can be disrupting. There are no absolute indications for continuous steroid therapy, and the decision to initiate it should be made only after careful consideration of the severity of the illness, its effect on the patient and the significant risks involved.

The presence of emotional factors influences the course of disease in any chronic illness and many children with chronic asthma have disturbed personal and family relationships which seem to affect the disease process. Dubo and coworkers,[21] however, were unable to correlate the severity of parent-child disturbed emotional patterns with severity and course of the child's asthma. Steroids which improve the child's respiratory symptoms and relieve the emotional tensions resulting from asthma will have no effect on other primary psychogenic disturbances. In some cases, putting the asthmatic child into a rehabilitation center may be wiser than prolonged steroid therapy.[7] Although nearly all children at these centers are receiving steroid therapy on arrival, a significant number are weaned from the drugs during their stay. It is also often found advisable for the parents to receive psychiatric help while the child is away from home.

Therapeutic Regimen

When a decision is made to use corticoid therapy, the type of treatment regimen must be determined. Careful follow-up is mandatory and the problems of adrenal suppression and growth inhibition must be kept in mind. In normal persons, there is a diurnal variation in spontaneous adrenal cortical activity, with the peak in hydroxycorticoid output between midnight and 8 a.m.[18] With small daily doses of exogenous corticoids there will be less adrenal suppression if the entire dose is administered between 8 and 10 a.m. rather than every 6 hours. Exogenous steroids administered "around the clock" in amounts less than the normal daily output will inhibit adrenal function. When long-term steroid therapy is being discontinued, a gradual tapering off will help to minimize the aggravation of symptoms that may occur until the patient's own pituitary-adrenal axis recovers.

An intermittent steroid schedule (given on three successive days of the week, then stopping for four days) has been used extensively in the management of nephrosis.[9] However, Siegel and coworkers,[53] who used this regimen in a group of allergic children with good results, still found evidence of adrenal suppression on the fourth day off therapy. Harter and coworkers[33] gave one large dose of prednisone every 48 hours before breakfast to a group of 58 adult patients (many of whom had asthma), this dose being the total amount required ordinarily over a two-day period for relief of symptoms. Adrenal suppressive action of the drug was gone after the first 24 hours and the pituitary-adrenal axis returned to normal in the second 24 hours. The anti-inflammatory effect of the drug, however, usually carried the patient through the entire 48-hour period. Harter[34] recently reported that the administration of ACTH injections once a month improved the efficiency of the 48-hour regimen, in some cases permitting reduction of the prednisone dosage. Siegel and coworkers[55] administered betamethasone to a group of asthmatic children at 48-hour intervals and, contrary to the work by Harter's group, demonstrated the occurrence of adrenal suppression in all subjects. Thus, more studies need to be done, using different steroid preparations, since there may be some discrepancy between the anti-inflammatory potency and adrenal suppressive action of the synthetic corticoids. Studies on the growth patterns of children receiving steroids at 48-hour intervals have not been reported.

Steroids administered by inhalation in the form of dexamethasone aerosols can often control symptoms at a dosage level less than that required with oral medication, and in some patients they are the most effective.[15] It was hoped at first that steroid inhalation therapy would circumvent some of the hazards of the corticoids, but adrenal suppression has also been demonstrated in patients receiving aerosols.[54] Parents must be informed of the difference between a steroid and a regular bronchodilator aerosol and should supervise its administration. In the University of California pediatric allergy clinic, where 200 new patients are seen each year with allergic problems of all degrees of severity, six patients are currently receiving long-term steroid therapy. Three of them are receiving dexamethasone aerosols (three to nine puffs per day), and three are receiving prednisone (5 to 20 mg at 48-hour intervals).

It is not necessary to suppress all allergic symptoms at the expense of high steroid dosage. The dose, in conjunction with standard bronchodilator therapy, should enable the child to carry on normal activity. The parents, however, must know the type and dose of medication the child receives so that in the event of emergency this information can be given to attending medical personnel. In acute stressful situations supplementary exogenous steroids may be necessary.

Regular efforts should be made to reduce the dose. The entire regimen of treatment for allergic disease should be reviewed periodically since there is a tendency for the family to make compromises when the child's clinical symptoms improve. Above all, the child must be closely observed for six to twelve months after the drugs are discontinued, keeping in mind all of the complications of steroid therapy.

In general, the results of prolonged steroid therapy as measured by relief of allergic symptoms have been good. In the series that have been reported, however, the criteria for the initiation of long-term therapy with steroids, and the concomitant allergic regimen, are not always well defined.[41,56,61] There have been conflicting reports regarding prognosis in asthma since the introduction of these agents. Some investigators feel that the morbidity and mortality have both declined[1]; others think that the morbidity has lessened but the mortality has increased.[48]

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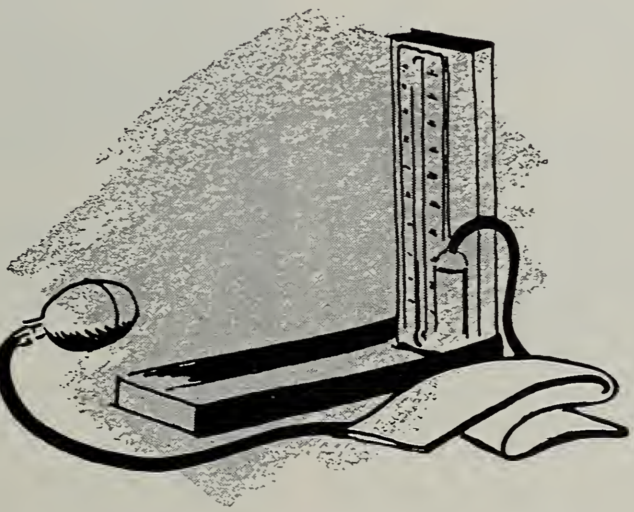

CASE REPORTS

Metastasizing Adenocarcinomas of the Tarsal Glands

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ADENOCARCINOMAS arising from the skin appendages of the eyelids are rare. Most of the tumors at that site reported in the literature are sebaceous gland carcinomas arising from meibomian glands and very few are carcinomas of sweat glands or the glands of Moll. Sweat gland carcinomas are much more common than sebaceous gland carcinomas in other areas in the skin, but most sebaceous gland carcinomas occur in the eyelid. Due to a considerable variance in the reported criteria and terminology, and because many of the tumors are very well differentiated, it is difficult to determine the exact number of cases of tarsal gland carcinomas in the literature. In this review, we included all adenocarcinomas that were primary in the eyelid and that had metastasized and therefore could be accepted as being malignant. This review was undertaken when we observed a case, the clinical features of which conform to those described for some sebaceous gland carcinomas, but the pathologic pattern of which was unusual, suggesting an origin in the glands of Moll.

Report of a Case

A 64-year-old Caucasian man entered the hospital on January 26, 1964, because of a mass in the right lower eyelid of four years' duration. He had consulted an ophthalmologist, not long before, because of "rapid growth." A biopsy specimen appeared benign on pathologic examination, but because of the increasing size of the lesion complete excision was recommended.

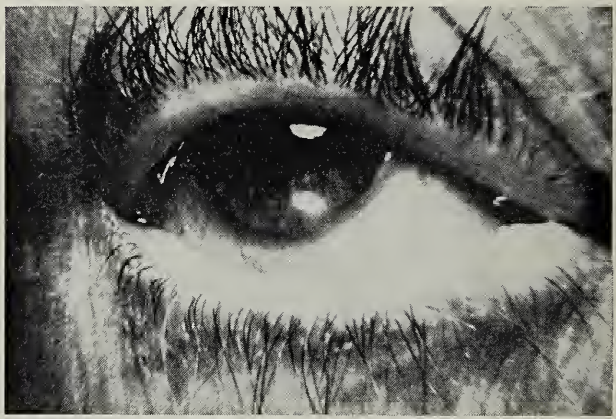

Figure 1.—Appearance of tumor before excision (Courtesy, Dr. S. Castanares).

On examination of the eyes a site of peripheral iridectomy was noted on the left eye. There was a 3 mm tumor on the right lower eyelid involving the palpebral margin, the skin adjacent to the palpebral margin and the conjunctiva. On January 27, 1964, under block anesthesia, a complete through-and-through wedge excision of the tumor-containing portion of the right lower lid was performed. The excision included the skin, orbicularis, tarsus and conjunctiva. A lateral canthoplastic lid reconstruction then was carried out.

Pathologist's report: The resected specimen was a wedge-shaped portion of the eyelid measuring 0.7 cm in greatest dimension. On the lid margin there was a 0.3 cm, flat, smooth, gray lesion extending into the underlying stroma. Microscopically, the small tumor was found to be lobulated, to extend close to the overlying epidermis, but to penetrate fairly deeply into the underlying stroma, partially surrounding hair follicles and meibomian

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glands. The tumor was papillary and microcystic, the individual delicate papillary processes being covered by single and occasionally multiple layers of cuboidal epithelial cells with very uniform, round and oval nuclei and a prominently vacuolated cytoplasm, the individual vacuoles being small and confluent. The tumor was locally completely excised, and was considered to be a papillary adenoma of sweat gland origin.

The patient was next admitted on August 24, 1964, because of a mass in the right pre-auricular area which he had noted three years previously, but which had become progressively larger over the past six months. This pre-auricular mass was not described on his admission in January 1964, but was noted by one examiner as a "right, pre-auricular, firm, freely movable mass" on his admission in October 1963, for a cataract extraction of the left eye. The physical examination showed a 2 × 4 cm soft, freely movable, right pre-auricular mass and was otherwise unremarkable. The preoperative diagnosis was probable right parotid tumor. On August 25, 1964, under general anesthesia, a 2 × 4 cm, gray, cystic mass was excised. It appeared to be adjacent to the parotid gland and was removed easily with blunt dissection. The patient was discharged on August 29, 1964.

The excised specimen consisted of two multilocular, lobulated, intact cystic structures measuring 3.8 × 3.0 and 2.6 × 2.0 cm. Sections showed the individual cystic compartments to measure up to 2 cm in diameter and to contain yellowish, cloudy, slightly mucoid fluid. The walls of the individual cystic compartments were thin and semitranslucent. A frozen section showed an epithelial, in areas papillary, cyst lining. The subsequent microscopic examination showed the individual cystic compartments to be lined by single and multiple layers of epithelial cells, most of which contained round or oval hyperchromatic nuclei and prominent clear vacuoles in the cytoplasm. In portions of the wall, there were solid nests and groups of glands formed by similar or occasionally more anaplastic epithelial cells with large nuclei and more prominent nucleoli. Papillary structures formed by these cells extended into individual cystic compartments. The compartments were surrounded by fibrous connective tissue septa which were slightly infiltrated by lymphocytes. The tumor was located within parotid tissue of which a rim was seen in the periphery. However, several of the nests of cystic and glandular structures were found within lymphoid tissue, indicating that the tumor was metastatic to a lymph node rather than a salivary gland tumor. The histologic pattern was very similar to that previously seen in the tumor of the right lower eyelid.

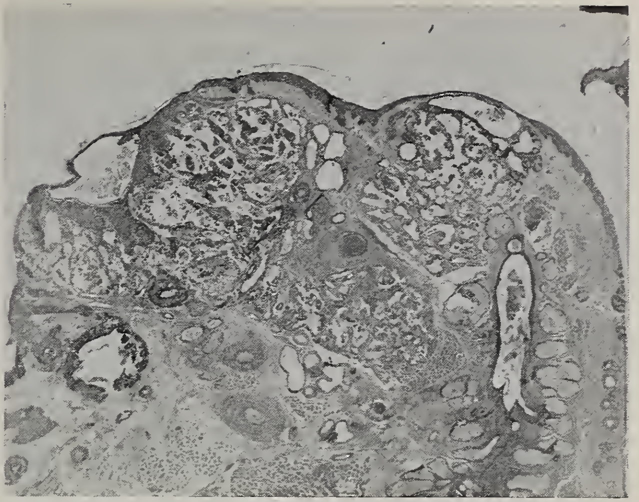

Figure 2.—Photomicrograph (× 30) showing the entire excised tumor from the eyelid. Note the papillary features and close proximity to many of the specialized skin appendages.

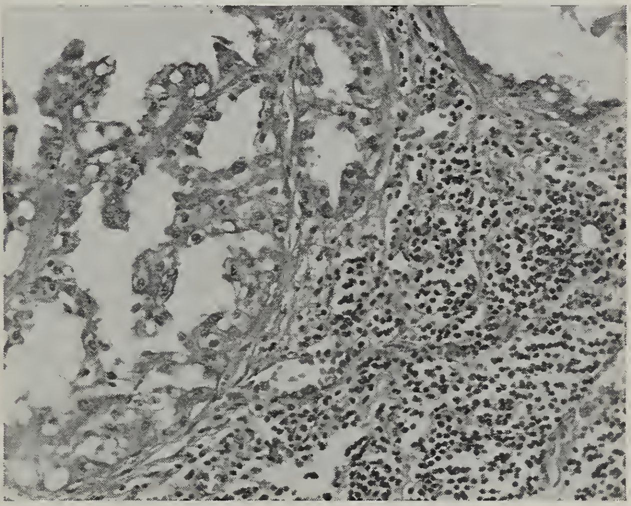

Figure 3.—Photomicrograph (× 250) of the metastatic lesion in pre-auricular lymph nodes. The typical histologic pattern with a prominently foamy cytoplasm of many of the cells is demonstrated.

Discussion

The pathologic features in the present case were unusual; they did not resemble those previously described in skin appendage carcinomas of the eyelid. The foamy cytoplasm and the overall cytologic appearance resembled those of sebaceous gland carcinoma. However, the papillary configuration and the cyst formation, more prominent in the pre-auricular lymph node metastasis than in the primary tumor were features more commonly seen in apocrine adenocarcinomas of sweat gland origin, and the tumor was interpreted (by Dr. Elson B. Helwig of the Armed Forces Institute of Pathology) as an apocrine adenocarcinoma of glands of Moll. There was, however, no resemblance of the pattern to that described in the very few references of carcinoma supposedly arising from the glands of Moll. Whorton and Patterson[23] described a case in which they demonstrated a transition from glands of Moll to tumor, but the described tumor itself was characterized by the occurrence of the tumor cells in the forms of cords and a solid pattern, quite contrary to the cystic and somewhat papillary pattern seen in the present case. Since origin of the tumor from glands of Moll was not unequivocally demonstrated, and as the histologic features conformed neither to the described meibomian gland carcinomas or the rare carcinomas of the glands of Moll, we prefer to classify the lesion simply as an adenocarcinoma of specialized tarsal glands.

Clinically, the case did have features similar to those reported in several of the cases of carcinoma of tarsal glands collected in the literature, as noted in Table 1. All cases of adenocarcinoma of the eyelid apparently arising in skin appendages, in which there was definite evidence of malignancy as shown by metastasis, are included.

Of the 15 previously reported cases with known metastasis from tarsal gland adenocarcinoma, nine were reported as arising in meibomian glands. Five cases were reported as either sebaceous or tarsal gland carcinoma without note as to specific origin. The primary tumor site was in the upper lid in nine cases, in the lower lid in four; and in three cases the site was not stated. This predilection for the upper lid is consistent with the greater number of meibomian glands in the upper than in the lower lids.[19] Stout and Cooley[20] described a case involving the sweat glands of the eyelid with metastasis, but so far as we could determine there have been no reported cases of metastasis of tumors of the glands of Zeis or Moll. In a case reported by Whorton and Patterson[23] of an apparent carcinoma of Moll's glands, there was associated extramammary Paget's disease of the overlying skin as well as a palpable parotid lymph node, which subsequently, however, disappeared. There was no mention of metastasis in Scheie's[15] case of adenocarcinoma of the glands of Zeis. The latter two cases were, therefore, not included in our tabulation.

As was noted by Straatsma,[19] the pre-auricular or parotid lymph nodes are the most frequent sites of metastasis (nine of sixteen cases). Supraclavicular, cervical or submaxillary nodes may be involved. Distant metastasis also occurs, however.[8,10,20]

It is interesting that our patient noted the eyelid tumor four years before admission, and the pre-auricular nodes six months later, but the onset of progressive enlargement of the metastatic lesion did not occur until the primary tumor had been removed. An accelerated rate of growth after incomplete excision or curettage with early recurrences and metastasis has been described by other observers.[4,19,21] The primary tumor in our patient, however, had been completely excised following the initial biopsy.

To distinguish tarsal gland adenocarcinomas from a chalazion may be very difficult.[3,5,14] The importance of this distinction and the awareness that the combination of a pre-auricular, parotid or cervical mass and a small "chalazion" may represent tarsal gland carcinoma with metastasis, has been emphasized.[6,19,21]

The prognosis for tarsal gland carcinoma is unfavorable once metastasis has occurred. At the time of publication of the reports of the 16 cases reviewed, seven of the patients had died of metastatic disease. The cases as selected represent the least favorable group of tarsal gland carcinomas, since metastasis had already occurred, but most of the tumors were very well differentiated and some had a long course up until the time of biopsy or excision, as was the case in the patient herein reported upon. Subsequent to diagnosis and excision, rapid recurrence and local extension were often noted.[1,20,24] Orbital exenteration was required in at least three cases. All patients had been treated with surgical excision and some with subsequent radiotherapy. Only two patients were followed for an extended period, one of them surviving for 11 years,[10] and one being alive and well 15 years after excision of both the primary tumor and the lymph node metastastic lesion and subsequent radiotherapy.[12]

Summary

A case of tarsal gland adenocarcinoma in a 64-year-old male is described. The primary tumor in the right lower eyelid was quite small and was

TABLE 1.—*Clinical Data on 16 Cases of Adenocarcinomas of Tarsal Glands*

Author	*Year*	*Sex and Age*	*Duration of Symptoms*	*Type and Site of Primary Tumor*	*Site of Metastasis*	*Treatment*	*Follow-Up*	*Remarks*
Sourdille[17]	1894	M-59	....	Sebaceous gland carcinoma, upper eyelid	Preauricular lymph nodes	Curettage	....	Rapid growth-recurrence 12 days after curettage
Snell[16]	1908	F-63	10 years	Meibomian gland carcinoma, upper eyelid	....	Excision exenteration	....	Recurrence with metastasis even after exenteration
Cavara[2]	1920	M-67	Few months	Sebaceous gland carcinoma, upper eyelid	Preauricular lymph nodes	Exenteration with lymph node excision	Died of tumor	Recurrence 6 months postoperatively
Hagedoorn[6]	1934	M-66	2 years	Meibomian gland adenocarcinoma, upper eyelid	Preauricular and supraclavicular lymph nodes	Excision	Died of tumor	Nodes excised 4 years after removal of primary. Died 4 months postoperatively
Knapp[8]	1936	F-59	....	Meibomian gland adenocarcinoma, upper eyelid	Preauricular and nodes on side of face and neck, abdominal tumor	Excision, radium	Died of tumor	....
Pages et al.[13]	1938	M-33	3 weeks	Sebaceous gland carcinoma	....	Excision, x-ray therapy	....	Metastasis present at operation. Recurrence and metastasis disappeared with x-ray therapy
Magnus[10]	1947	M-79	11 years	Meibomian gland adenocarcinoma, lower eyelid	Liver	Excision	Died of tumor	Had "ulcerated tumor" removed right lower lid 11 years prior to death. No pathology report of specimen
Spaeth[18]	1951	......	....	Adenocarcinoma tarsus	Cervical and submaxillary glands	....	....	....
Spaeth[18]	1951	......	....	Adenocarcinoma, tarsus	Lip with extension to nose and malar bone	....	Died	....
Ibrahim[7]	1951	M-73	1 year	Meibomian gland adenocarcinoma, upper tarsus	Preauricular node	Excision, postoperative irradiation	1 year	Node excised 6 months after removal of primary
Stout and Cooley[20]	1951	F-44	2 months	Sweat gland carcinoma, lower eyelid	Ethmoid bone, lung	Excision, x-ray therapy, exenteration	Died	Exenteration after 2 re-excisions and x-ray therapy. Died 2 years after onset and 22 months after first operation
Straatsma[19]	1956	......	....	Meibomian gland carcinoma, upper eyelid	Preauricular lymph node	Excision	15 years	Postoperative radiation therapy, primary lesion and node excised simultaneously
Sweebe and Cogan[21]	1959	F-64	6 months	Meibomian gland adenocarcinoma, lower eyelid	Orbit preauricular node	Excision radical neck dissection 6 months later	Died	Died of cardiac failure 36 hours after radical neck dissection
Sweebe and Cogan[21]	1959	M-79	....	Meibomian gland adenocarcinoma, upper eyelid	Preauricular and cervical lymph nodes	Excision of mass and nodes	Died	Lost 30 pounds 7 months after excision. 7 months postoperatively had large mass palpable in right upper quadrant. No autopsy
Mangubat and Garcia[11]	1961	F-62	2 years	Meibomian gland carcinoma, upper eyelid	Regional lymph nodes	Excision postoperative radiation	....	....
Gowey and Kern	1965	M-64	4 years	Tarsal gland adenocarcinoma, lower eyelid	Preauricular lymph nodes	Excision		Rapid growth of preauricular lymph node after biopsy and subsequent excision of primary tumor

completely excised, but metastasis to right pre-auricular lymph nodes had occurred. In a review of the literature reports were found of 15 similar cases of tarsal gland carcinoma, most of which had originated in meibomian glands. Because of the high incidence of metastasis, a diagnosis of tarsal gland carcinoma should be considered in patients with often small tumors in the eyelid, particuarly in the presence of palpable pre-auricular nodes.

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Sporotrichosis in California

ERVIN EPSTEIN, M.D.
Oakland

Speed and ease of travel may result in the transplantation of endemic diseases into new areas. In some instances, the causative organism may be transported in products, baggage or vehicles. In others, prolonged incubation periods may result in the appearance of manifestations of the disease long after the patient has departed from the geographic area in which he was infected. For instance, Harrell and Honeycutt reported on 12 patients who acquired coccidioidomycosis in California or Arizona but in whom the infection was diagnosed in southeastern Michigan.[3]

Sporotrichosis is endemic in the midwest, especially in the Mississippi Valley. According to Phillips and Baritel,[4] seven patients with this disease had been reported from California up to January 1, 1947, out of 256 recorded cases of this mycosis. No further reports of sporotrichosis in California were uncovered after that date. In fact, the only other mention of this infection in this state was in an investigative article from Los Angeles discussing the distribution of I^{131} in lesions of sporotrichosis produced experimentally in mice.[5]

In most of the seven patients, it was impossible to trace the source of infection. Unknown to the physicians reporting the case, one patient had returned from a camping trip in the Mississippi Valley not long before the disease was diagnosed. The following patient is presented as an example of sporotrichosis of industrial origin in which the infection, diagnosis and cure occurred within the boundaries of California. Of course, the assumed source of the infection (a cat) may have reached California from a recognized endemic area. A similar case of sporotrichosis due to the bite of a cat that was being destroyed was reported by Conkwright.[2]

From the Departments of Dermatology, University of California School of Medicine, San Francisco, California; and Highland-Alameda County Hospital, Oakland, California.

Submitted November 16, 1964.

Report of a Case

The patient was a 21-year-old white man who was employed by the Society for the Prevention of Cruelty to Animals. One of his duties was the destruction of unclaimed stray animals. On February 11, 1958, while disposing of a stray cat that resisted his efforts, he was scratched or bitten on his right thumb. The laceration did not heal over a period of several months. Slowly the traumatized area became purulent, ulcerated and crusted. It extended to involve an area the size of a silver dollar. Within one month, deep nodules developed along the flexor surface of the right forearm. On examination on April 18, 1958, a large deep ulcer over the proximal joint of the right thumb was noted. It was filled with clean granulation tissue. The borders were raised, purplish and indurated. Pipestem lymphangitis extended from the ulcer to the right axilla. Firm erythematous intracutaneous and subcutaneous nodules were interspersed along the path of lymphangitis. The clinical diagnosis was sporotrichosis and this was confirmed by the cultural isolation and identification of *S.schenkii* from the chancre. Therapy with potassium iodide by mouth resulted in complete cure within one month.

Comment

Sporotrichosis is encountered infrequently in California. While it hardly seems necessary to offer a textbook description of so well-known an entity in this short report, it behooves the local physicians to become acquainted with the characteristic chancre at the site of inoculation followed by the development of nodules along the course of the lymphatic channels serving the area. Unfortunately, this pattern may be simulated by other granulomatous infections. Furthermore, I studied a patient with an arsenic-caused squamous cell epithelioma of the hand in whom metastasis developed along the lymphatic channels, thereby mimicking sporotrichosis. Also, sporotrichosis does not in all instances present the features that have been mentioned here.

According to Browne,[1] the Bacteriology and Mycology Laboratory of the California State Department of Public Health encountered only four examples of sporotrichosis during the 10 year period between 1948 and May 1958. One of these was the case reported herein. To convey some idea of the volume of work performed in this laboratory, 1,069 specimens were examined for fungi during the year 1957.

To date, sporotrichosis can be considered to be a curiousity in California. Of course, there is no reason why this infection could not be contracted in this state. Rapid transportation, adding the factor of infected persons visiting or migrating from the Midwest to California, may make it more common in the future.

Summary

In the case here reported, a man became infected with *S.schenkii* in California far from the endemic area.

With ease and speed of present day travel, endemic diseases may be encountered any place in the world.

447 29th Street, Oakland, California 94609.

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Second Attacks of Meningococcal Meningitis

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San Diego

IT IS STATED that second attacks of meningococcal infection are rare, and that an infection may even confer some immunity.[1] However, recent Navy experience in the San Diego, California, area suggests that individuals who have had meningococcal meningitis may have a high risk of recurrence, as illustrated by the following reports of two recent cases of proved second attacks of meningococcal meningitis in enlisted men.

Reports of Cases

CASE 1. An 18-year-old Caucasian male had completed his first month of recruit training at San Diego when he was put in hospital on November 15, 1961 because of frontal headache, lethargy and myalgia for one day.

On physical examination, temperature of 102°F, slight meningismus, pharyngeal injection, positive Brudzinski's sign and a generalized petechial rash with some ecchymotic areas were noted. Spinal fluid was obtained under normal pressure, and contained 44 mg of protein and 105 mg of sugar per 100 ml and 114 mEq of chlorides per liter. There were only 3 neutrophils and 4 lymphocytes per cu mm, but a Gram-stained specimen showed intracellular and extracellular Gram-negative diplococci. A chocolate agar plate culture of spinal fluid grew *N. meningitidis;* unfortunately, serological typing of the organism was not performed. Blood cultures were negative for pathogenic organisms.

The patient became comatose the day of admission despite intravenous administration of sulfadiazine and penicillin. He regained consciousness on the second hospital day and, although he complained of severe retrobulbar headache for the next six days, there was good response to continuous antibiotic treatment and he was discharged to full duty on December 6, 1961.

Between 1961 and 1964 he had excellent health. He served aboard a destroyer as an engineman-fireman, made one cruise to the Orient, and was married in 1962. At 1800 on July 24, 1964, while aboard ship in San Diego harbor, he began to have chills and fever and was awakened twice during the night because of nausea, with a single episode of vomiting. The following morning, at sick call, he complained of pain on moving his legs.

He was immediately put in hospital, being admitted at 1000 on July 25, 1964. On admission he was alert and responsive but complained of generalized myalgia and "burning" in both legs. On physical examination petechiae were seen over the entire body, including the oral and conjunctival mucosae, and there were large patches of eccymosis on the legs. Nuchal rigidity was not detected, and the blood pressure and temperature were normal.

Leukocytes numbered 33,400 per cu mm with over 90 per cent immature neutrophils. On lumbar puncture the opening pressure was 250 mm of water. There were only 12 cells per cu mm of spinal fluid, but it contained 118 mg of protein per 100 ml. A Gram-stained specimen of the spinal fluid showed Gram-negative diplococci, later proven to be group B meningococci resistant to 5 mg of sulfadiazine per 100 ml *in vitro*. Three cultures of blood taken on the day of admission also grew this organism.

Despite treatment, including intravenous fluids and antibiotics, use of hypothermia, vasopressors and, later, steroids, the condition of the patient worsened rapidly and he died July 31. Of particular interest was the development of fever of 108°F on the second day in hospital, accompanied by a fall in blood pressure despite the use of intravenous vasopressors.

On autopsy multiple hemorrhages in the internal organs were noted, including the adrenal cortex (Waterhouse-Friderichsen syndrome).

From the U.S. Navy Preventive Medicine Unit No. 5, U.S. Naval Hospital, San Diego.

From Research Project MR 005.09-1215, Bureau of Medicine and Surgery, Washington, D.C., 20390. The opinions and assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

Submitted January 21, 1965.

CASE 2. A 19-year-old Caucasian recruit had been in training at San Diego for one week when chills and fever developed the evening of December 14, 1960. The next morning he complained of severe frontal headache. Rectal temperature was 101°F.

When admitted to hospital at 1000 on December 15 the patient was lethargic and lying with the neck extended and heels drawn down. He answered questions slowly but accurately. On physical examination, pronounced nuchal rigidity, blurring of the right optic disc, and positive Kernig's and Brudzinski's signs were noted. On lumbar puncture the opening pressure was 420 mm of water. The spinal fluid contained 249 mg of protein and 50 mg of sugar per 100 ml and 2,000 cells per cu mm, of which 97 per cent were neutrophils. Gram-negative diplococci were seen on smears of the spinal fluid, and a culture grew *N. meningitidis,* type not determined. Blood cultures were negative for pathogenic organisms.

The patient responded well to treatment with intravenous penicillin, sulfadiazine and chloramphenicol and was discharged to full duty with no sequellae on January 26, 1961.

He completed recruit training and served aboard an aircraft carrier without incident until June 12, 1964, when he had sudden onset of fever, chills and generalized myalgia. Upon reporting to the ship's sick bay that afternoon he complained of pain and soreness of the upper back. Since obvious meningismus was noted on physical examination and the temperature was 104.8°F orally, he was immediately put in hospital.

On physical examination the pulse rate was 115 and the blood pressure 106/58 mm of mercury. Nuchal rigidity and multiple petechiae were noted. On spinal puncture the opening pressure was 190 mm of water. Clear spinal fluid was obtained. It contained 26 mg of protein and 58 mg of sugar per 100 ml, and no cells. However, cultures of the fluid later grew *N. meningitidis,* type B, resistant to over 10 mg of sulfadiazine per 100 ml *in vitro.* This organism was also grown on cultures of blood taken the day after admission. Serum protein electrophoresis was normal with 3.9 gm of albumin and 3.4 gm of globulin per 100 ml.

Despite vigorous intravenous administration of sulfadiazine, penicillin and choramphenicol, and maintenance of the blood pressure with metaraminol, the patient remained in serious condition. On the day after admission he became oliguric and large areas of eccymosis appeared on both the upper and lower extremities. On the third hospital day, however, urine output increased and he became more responsive. On examination of the urine at that time, microscopic hematuria and abundant granular casts were noted. On the sixth hospital day it was possible to discontinue intravenous fluids and medications, but many of the peripheral eccymotic areas had become gangrenous, necessitating subsequent amputation of two toes of the left foot, and leaving several large denuded areas on the lateral aspects of both legs. In October 1964, the patient was completely asymptomatic and was transferred to another hospital for completion of skin grafting procedures.

Discussion

The occurrence of fulminating second attacks of disease in these two men suggested an unusual lack of resistance to meningococcal infections, since the overall incidence of meningococcal infection in this area is low. Between June 1963 and October 1964, there were only eight other cases of meningococcal meningitis (exclusive of recruits) among approximately 70,000 active duty personnel in this naval district. Interestingly, one of the eight also had recurrent meningitis but that case is not included in the present report since only six months elapsed between attacks, and "chronic meningococcemia" could not be ruled out. In addition, one of 14 recruits who had meningococcal meningitis during this period also had a second attack four months after the first. Between December of 1960 and of 1961, when the two patients herein reported upon first had the disease as recruits, approximately 50,000 other men were processed through recruit camp with only nine other cases among them.

It was possible, of course, that the reported cases were caused by either overwhelming exposure or by contact with exceptionally virulent strains of meningococci. The former seems unlikely since neither of the men had been subjected to undue stress and since meningococcal carrier rates among their shipmates were well within normal limits. On the destroyer, positive cultures for meningococci were obtained from the nasopharynx in six of 57 men (10.6 per cent), while on the aircraft carrier there were eight positives in 146 cultures (5.5 per cent). The meningococci isolated from the two patients in the present cases were not unusual: group B sulfadiazine resistant strains are at present the predominant meningococci in this area.[2] Since January 1, 1964 we have examined isolates from 19 cases of meningococcal meningitis in San Diego: all were group B and 16 were resistant to sulfadiazine *in vitro*. In addition, over 70 per cent of meningococci isolated from normal carriers in this area have proven to be group B and resistant to sulfadiazine.

Because of the difficulty in collecting data on other cases of meningococcal meningitis in adults outside this naval district, it is possible that recurrent disease is more common than was assumed previously. Since there was no evidence of debility or unusual stress in the two cases herein reported (or in two other cases in navy personnel in this area with shorter periods between attacks) it is possible that the patients lacked a "natural immunity" to meningococcal infection. At least in Case 2, in which serum protein electrophoresis was performed, lack of resistance was not due to hypogammaglobinemia.

Summary

The occurrence of second attacks of meningococcal meningitis in two Navy enlisted men is described. It is suggested that the patients may have lacked natural resistance to meningococcal infection.

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California Medicine

EDITORIAL

Another Legislative Year

ANOTHER SESSION of California's state Legislature has come to a close, although the process of winding up this year's business required a special session called immediately on the adjournment of the 120-day legal session which convened in January.

On top of that, another special session in the fall appears more than a possibility.

California's system of legislation calls for the 80-member Assembly and the 40-member Senate to meet in odd-numbered years for the consideration of general legislative topics and in even-numbered years for consideration of a budget for the coming fiscal year. In addition, the Governor may call a special session to be held before or after a regular session or even concurrently with it. Where special sessions are called they may deal only with the topics specified by the Governor in his call.

The Legislature this year was as burdened as in past years with proposed bills. More than six thousand measures were introduced into the two houses of the body and, as usual, about one in ten had some bearing on the public health or the practice of the healing arts.

CMA's Committee on Legislation has already reported to the membership on the measures entrusted to it for passage. In all, 21 bills were introduced under CMA sponsorship. Of these, 15 were passed by the Legislature and sent to the Governor for signature. Three of the measures not passed were referred to interim committees for study, two were not even considered in committee and one was combined into another bill which was passed.

This good record on the positive side was more than matched in the opposite direction, when nearly all measures opposed by the CMA were either defeated or assigned to interim study. The overall batting average ran quite high and the elected officials of the Association are well pleased with the year's results.

Among the major measures approved by the Legislature were several bills designed to tighten up on discipline for erring physicians. In brief, these bills will create a series of regional review committees which will work with the State Board of Medical Examiners in reviewing reported cases of medical practices not in the public interest which today are difficult to deal with adequately under the law as administered by the medical examiners or the code of ethics as handled by component medical societies. The review committees would be appointed from nominees selected by medical societies, by medical schools and by the Board of Medical Examiners. Three of the five members of each committee would be nominees of the medical societies in the region, so that the practicing physicians of the area would represent the major element of the committee.

Review committees would investigate and hear reported cases of medical incompetence, mental incompetence or other shortcomings which are not listed in the Medical Practice Act as subject to discipline for professional misconduct and which are not violations of the Principles of Medical Ethics and subject to medical society discipline. The physician who undertakes procedures beyond his capacity, or those for which he is not adequately trained, the physician who is suffering from a disturbed mental condition and is not confined, would come under the provisions of the new laws. The practical outlook of committee members named by the medical society of the region would assure a down-to-earth approach by these committees and eliminate an ivory-tower or theoretical handling of the cases brought before the group.

At the same time, the members of the review committees would be shielded from civil suits brought by those who are called to appear in explanation of their actions.

This type of legislation has been developed over a period of years of discussion and holds every promise of bridging a gap in the processes for halting practices not in the public interest.

Another measure promoted by the Association and given lengthy hearings by the Legislature was Assembly Bill 760, introduced by Assemblyman Jack T. Casey of Bakersfield. This bill would have modified the present laws for providing medical services to the needy aged under the federal Kerr-Mills and the state Rattigan laws. While this bill was amended on numerous occasions, it survived in a form acceptable to CMA leaders but was not adopted during the regular or the special session of the Legislature. Instead, it was ordered out for interim study but the Governor has indicated his desire to have it reconsidered by a special session of the Legislature in the fall months, following the anticipated enactment of federal Medicare legislation. This bill would provide a more realistic handling of medical care for the needy aged and would attract additional federal funds which would ease the financial burden on the state and county governments.

The Public Health League of California was again functioning in behalf of its members during the 1965 session, with the advantage this year of having a business office located only yards away from the State Capitol. The benefits of this office, in contrast to former operations from a hotel suite, have been obvious to all those with intimate knowledge of legislative dealing and responsibilities.

The California Medical Association once more owes a deep debt of gratitude to its Committee on Legislation and the representatives of the Public Health League. These people have devoted their time, efforts and talents to maintaining and acquiring proper legislation for the members of the Association, and their accomplishments are deserving of acclaim.

California Medical Association

NOTICES AND REPORTS

Council Meeting Minutes

Tentative Draft: Minutes of the 512th Meeting of the Council, San Francisco, Hilton Inn, June 12, 1965.

The meeting was called to order by chairman Anderson in the Hilton Inn, San Francisco International Airport, on Saturday, June 12, 1965, at 9:30 a.m.

Roll Call

Present were President Teall, President-Elect MacLaggan, Speaker Quinn, Vice-Speaker Telford, Secretary Hosmer and Councilors Isenhour, Wilson, Melone, Todd, Gooel, Taw, Bullock, O'Connor, Ham, Rogers, Burnett, Richard S. Wilbur, Miller, Watts, Fenlon, Kay, Anderson, Yant, Grunigen and Shaw.

Absent for cause, Editor Dwight L. Wilbur, Councilors Maguire and Kaiser, Past President Doyle.

A quorum present and acting.

Present by invitation were Messrs. Hunton, Thomas, Collins, Eberlein, Moreillon, Whelan, Edwards and Bowman, Doctor Miller, Mmes. Griffith and Redfern and Miss Price of CMA staff; Messrs. Hassard and Huber of legal counsel; Messrs. Read and Brown of the Public Health League; county executives Scheuber of Alameda-Contra Costa, Rosenthal of Los Angeles, Blankfort of Marin, Colvin of Monterey, Nute of San Diego, Neick of San Francisco, Thompson of San Joaquin, Rideout of Butte-Glenn, Wood of San Mateo, Marvin of Santa Barbara and Donovan and Pearce of Santa Clara; Doctor H. C. Pulley of the State Department of Health; James V. Lowry, M.D., State Director of Mental Hygiene; Doctor Lester McDonald of the State Department of Social Welfare; Doctors William H. Thompson and T. Eric Reynolds and Messrs. Paolini, Wahlberg, Nyron, Heller, Potloff and O'Dea of California Physicians' Service; Messrs. Aubrey Gates and John Pompelli of the American Medical Association; Richard Layton of AMPAC; Robert F. Garrick, consultant; Doctors Henry Gibbons, III, Samuel R. Sherman, Warren L. Bostick, Donald House, B. Otis Cobb and others.

1. *Minutes for Approval*

On motion duly made and seconded, minutes of the 511th meeting of the Council, held May 8, 1965, were approved as presented.

2. *Membership*

(a) A report of membership as of June 9, 1965, was presented and ordered filed.

(b) On motion duly made and seconded, 748 delinquent members whose dues had been paid subsequent to the preceding meeting were voted reinstatement.

(c) On motion duly made and seconded in each instance, 15 applicants were voted into Associate Membership. These were: Thomas H. Hew-

RALPH C. TEALL, M.D.	President
JAMES C. MacLAGGAN, M.D.	President-Elect
WILLIAM F. QUINN, M.D.	Speaker
JOSEPH W. TELFORD, M.D.	Vice-Speaker
CARL E. ANDERSON, M.D.	Chairman of the Council
ALBERT G. MILLER, M.D.	Vice-Chairman of the Council
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lett, Harold M. Williams, Fresno County; Magdolna Bartok, Harry M. Nardini, Los Angeles County; Clyde Miller, Marin County; Lawrence Hart, Orange County; Don C. Littlefield, Riverside County; William C. Adams, San Diego County; Raymond C. Berggreen, Phillips Johnson, San Francisco County; Mary Ni, San Joaquin County; Esther Byberg, Santa Barbara County; Allen B. Barbour, LeRoy E. Bates, George D. Gulevich, Santa Clara County.

(d) On motion duly made and seconded in each instance, 11 applicants were voted into Retired Membership. These were: John Louis Lohse, Alameda-Contra Costa County; Ben R. Dysart, Los Angeles County; Jack C. Hill, San Bernardino County; Henry K. Albertson, Robert P. Weddle, San Diego County; C. Frederic Fluhmann, Genevieve F. Gaffney, A. S. Musante, San Francisco County; Anna F. Barnett, Santa Clara County; Samuel Vaughn Dragoo, Sonoma County; Edna F. Patterson, Yolo County.

(e) On motion duly made and seconded in each instance, 30 members were voted a reduction of dues because of postgraduate training or prolonged illness.

3. *Tribute to Deceased Members*

On motion duly made and seconded, it was voted to adjourn this meeting in the memory of Doctor William J. Kerr, long-time chief of the Department of Medicine at University of California School of Medicine, and Doctor Junius B. Harris, former president of the Association, Vice-President of the American Medical Association and chairman of the Association's legislative committee from 1928 to 1940.

4. *Report of the President*

President Teall detailed his recent appearance in Washington as the Association's witness before the Senate Committee on Finance in opposition to HR 6675. He also reported on the current status of AB 760 in the State Legislature and on other measures on which he had appeared as a witness.

Doctor Teall reported on a meeting with officers of the California Veterinary Medical Association and leaders of the state veterinary medical school and urged that continuing discussions take place on many items where a community of interest appears.

ACTION: Voted to refer continuing liaison with the California Veterinary Medical Association and veterinary teaching officials to the Committee on Other Professions for follow-up and later report.

Doctor Teall also reported on a meeting with the California Medical Assistants' Association and reported that organization's obvious desire to be of assistance to the CMA.

An AMA meeting in the fall on Medical Ethics and Professional Relation was reported and Doctor Teall suggested that Doctors Donald A. Charnock, James C. MacLaggan, Ralph C. Teall and Mr. Hassard be designated as CMA representatives, with additional or alternative names requested.

Doctor Teall further reported on a meeting with the officers of the California Hospital Association, at which a number of subjects, including payments to radiologists for in- or out-hospital services, were discussed.

ACTION: Voted to ask Committee on Committees to nominate a liaison group to meet with a similar committee from the California Hospital Association for an in-depth study of the problems brought out at the earlier meeting.

Doctor Teall finally reported that questions had been raised as to the Association's position on medical services on state and junior college campuses and pointed out that Council policy approved in January had called for the use of prepaid insurance mechanisms wherever possible. He asked that this position be clarified to show that basic medical services on state and junior college campuses be performed on campus and that the use of the insurance mechanism be followed for more serious conditions.

ACTION: Voted to reaffirm earlier position and indicate that the Association approves the performance of basic medical services on state and junior college campuses.

5. *Death of Past President J. B. Harris*

Doctor Teall reported on the recent death of Doctor Junius B. Harris, who had served as president of the Association, as vice-president of the American Medical Association and from 1928 to 1940 as chairman of the Association's Committee on Public Policy and Legislation. He proposed that a contribution of $100 be made to a fund being raised to secure an adequate memorial in Sacramento, that a suitable note of sympathy be sent to the family and that this meeting adjourn in Doctor Harris' memory.

ACTION: Voted to contribute $100 to a J. B. Harris memorial, to extend sympathies to his family and to adjourn this meeting in his memory.

ACTION: Voted to request the California Medical Education and Research Foundation to consider establishment of a Junius B. Harris Memorial Fund.

6. *State Department of Public Health*

Doctor H. C. Pulley, deputy director of the State Department of Public Health, reported that a resolution now before the Legislature calls on the department to develop procedures for the identification of rubella, possible preventive measures and methods of treatment for the benefit of physicians who are treating cases in pregnant women in their first trimester. The State Board of Health will consider this resolution in September and the department asks for conferences with the Association prior to that time.

ACTION: Referred to Committee on Public Health, in conjunction with Scientific Board the matter of conferences with State Department of Public Health on rubella.

Doctor Pulley also reported that the State Board of Health has proposed changes in its regulations to require the reporting of rubella and the isolation of active cases.

Doctor Pulley reported that a resolution in the Legislature asks for an augmented program by the department in the control of syphilis, including the use of available federal funds. He also reported an outbreak of salmonella typhimurium in Riverside County, now in its fourth week and involving about 10 per cent of the users of the community water system. Three deaths have been reported to date but most cases are light.

Doctor Pulley further reported that a plan has been developed for the follow-up of military draft rejectees. The plan envisages the use of interviewers at three draft stations and referral of rejectees for physical reasons to their physicians.

7. *State Department of Social Welfare*

Doctor Lester McDonald, medical director of the State Department of Social Welfare, reported that the department is working for the passage of AB 760, the Association-sponsored legislative measure to extend the insurance principle to the care of medical indigents.

8. *State Department of Mental Hygiene*

Doctor James V. Lowry, director of the State Department of Mental Hygiene, reported that following the Association's review of state hospitals, some progress had been noted in the State Legislature in improving conditions, including an approximate 50 per cent increase in appropriations for drugs. The department, he stated, will later ask the Association for assistance in evaluating staffing standards within the mental hospitals. Staff levels now approximate 80 per cent of the personnel standards set in 1952. State hospital occupancy, despite an increased admission rate, is now about 2,000 patients lower than a year ago.

9. *State Department of Finance*

The chairman read a letter from Mr. Ed Beach of the State Department of Finance, in which he stated that the department would appoint a CMA member to the Technical Advisory Committee. Another letter requested approval for the staffs of CMA and the Department to work together to define areas of study as called for in S.R. 111.

ACTION: Doctor Maurice S. Salomon of San Francisco appointed to serve on the Technical Advisory Committee.

ACTION: Voted to approve the staff cooperating with the Department and to report on appropriate conclusions for endorsement of the Council.

10. *Student Health Problems*

Doctor B. Otis Cobb reported on the progress of a study on student health problems and school performance. Some 1,800 students in the first, fifth and ninth grades have been examined to date in this study, which is financed by the California Dairy Council and which utilizes mobile trailers as examining sites. Doctor Cobb paid tribute to Councilors Kay and Ham for their cooperation in this study.

11. *American Medical Association*

Mr. Aubrey Gates, director of field services for the American Medical Association, expressed thanks for the cooperation of the CMA in national affairs and for the leadership supplied by California. He also thanked the CMA for its cooperation with Mr. John Pompelli of his staff, who is being transferred to Washington, D.C.

ACTION: The Council commended Mr. Pompelli and the staff was directed to secure a suitable memento in recognition of his cooperation with the Association during his tour of duty in California.

12. *California Physicians' Service*

Doctor William H. Thompson, chairman of the Board of Trustees of California Physicians' Service, gave a progress report on CPS activities, including studies going on on school health programs. He also reported that the trustees had further defined the duties of CPS President T. Eric Reynolds so as to utilize his talents to the best possible extent.

13. *Medical Executives Conference*

Mrs. Olive Neick, chairman of the Medical Executives Conference, reported on the meeting held June 11. She also reported that Everett Bannister, former chairman of the conference, would be united in holy wedlock on June 16. Staff was directed to send suitable congratulations to Mr. Bannister and his bride.

14. *Report of the President-Elect*

President-Elect MacLaggan reported on various meetings he had attended since the May meeting, including one at the State Department of Public Health concerned with the installation of automated equipment in a project known as California Health Information Planning Services. The plan would be financed by a National Institutes of Health grant and wound enable the department to maintain accurate statistics on the various personnel in all fields of health service. Doctor MacLaggan recommended that the Committee on Public Health follow the planning for this program.

ACTION: Voted to refer matter of CHIPS program to Committee on Public Health and that Chairman of the California Hospital Association liaison committee be invited to participate.

15. *Committee on Committees*

Chairman MacLaggan of the Committee on Committees offered the following nominations:

Advisory Committee to California College of Medicine—Forest J. Grunigen.

Medical Staff Survey Committee—add Doctors Robert Adams and Donald D. Lagerlof.

CMA-CHA Advisory Committee—Doctors Bert Halter, John T. Saidy, Joseph W. Telford, Glenn A. Pope and John Lundgren; Committee for Emergency Action to serve ex-officio.

Ad hoc Committee on Component Society Officers' Conference—William Dochterman and Olive Neick as consultants.

ACTION: Above nominations voted apprroval.

16. *Report of the Speaker*

Speaker Quinn reported on several meetings he had attended including that of the New Mexico State Medical Association and a meeting of peace officers in Santa Barbara. He also mentioned a bill now before the Legislature for the treatment of incipient narcotics addicts and stated that reports are now available on the successful operation of the narcotics hospital at Corona.

17. *Finance Committee*

Councilor Kay, chairman of the Finance Committee, reported the committee's approval of a $100 contribution to a memorial fund for Doctor Junius B. Harris in recognition of his contributions to the Association in legislative activities.

ACTION: Report of Committee approved.

Mr. Hassard outlined a request from the California State Chamber of Commerce for financial assistance in promoting a constitutional amendment to permit the California legislature to continue in its present format.

ACTION: Contribution of $1,000 approved to assist in State Chamber of Commerce drive to achieve constitutional amendment to permit state legislatures to maintain one house whose members are not elected on a population basis.

18. *Bureau of Research and Planning*

Chairman Sherman of the Bureau of Research and Planning, reported on a meeting with Doctor Michael DeBakey regarding the report of the President's Commission on Heart Disease, Cancer and Stroke and proposed that all state medical associations be urged to hold conferences on this report and to report their findings and recommendations to the executive vice-president of the American Medical Association for the information and guidance of AMA councils, commissions and trustees. He presented a draft of a resolution to this effect.

ACTION: Voted approval of resolution to be introduced into AMA House of Delegates to urge all state medical associations to hold conferences which would include medical educators and hospital administrators on the report of the President's Commission on Heart Disease, Cancer and Stroke and to report their findings and recommendations to the American Medical Association.

Doctor Sherman also reported that numerous requests for copies of the second progress report of the Committee on The Role of Medicine in Society had been received and that, in accordance with the Council's ruling, he was asking authority to fill two orders from out of state. These were for the American College of Physicians and the Ingraham County Medical Society in Lansing Michigan.

ACTION: Authority voted to fill above orders.

19. *Committee on Legislation*

Doctor Dan O. Kilroy, chairman of the Committee on Legislation, reported on a number of bills before the state Legislature. In view of the pending adjournment of the Legislature on June

18, he stated that a complete report on all items of interest to the Association would be prepared and distributed following the adjournment.

Doctor Bullock reported that Assembly Bill 2031 would require that female dogs secured from public pounds must be spayed within 30 days of their receipt by a new owner, a measure he described as aimed at legitimate research activities using dogs.

ACTION: Voted to oppose AB 2031.

20. *AMA Delegates*

President Teall reported that the Delegates to the AMA had reviewed a number of resolutions presented by the Council and the House of Delegates and was prepared to introduce them into the AMA House of Delegates. He also read a resolution submitted to the delegation asking for a study of the early appointments of hospital residents.

ACTION: Approval voted for introduction of resolution into AMA House of Delegates relating to study of early appointments for hospital residents.

21. *Commission on Public Agencies*

Councilor Miller, chairman, reported for the Commission on Public Agencies on several items:

(a) Asked approval to reprint copies of California mental health facilities report, distribution to be with consent of State Department of Mental Hygiene.

ACTION: Approval voted for reprinting report.

(b) House of Delegates resolution #18-65—commission recommended that CMA go on record as opposing use of lysergic acid diethylamide except by qualified investigators and accredited research facilities.

ACTION: Commission recommendation approved.

(c) House of Delegates resolution #36-65 relative to narcotic addiction—commission recommended that intent of resolution can best be carried out by publication in CALIFORNIA MEDICINE of an informative article on current developments, legislation and treatment programs.

ACTION: Commission recommendation approved with additional possible collaboration with the Committee on Dangerous Drugs.

(d) House of Delegates resolution #38-65 relative to a study of suicides—commission asked that Committee on Mental Health be authorized to establish a subcommittee to study subject and to confer with insurance and suicide prevention experts.

ACTION: Commission recommendation approved.

(e) Committee on Mental Health asked authority to use funds budgeted for a meeting of county society mental health committees for an alternate Congress on Mental Health in September.

ACTION: Use of budget funds for proposed congress approved.

22. *Commission on Community Health Services*

Chairman Kay of the Commission on Community Health Services reported that the circulation of *Health Tips* was now 1,839. He also presented a draft of a brochure on isometrics prepared by the Committee on the Medical Aspects of Sports and requested authority to proceed with its production and distribution.

ACTION: Brochure on isometrics referred to orthopedic consultants and Scientific Board for study and recommendations to Committee on the Medical Aspects of Sports.

Doctor Kay reported that the commission had been asked to conduct a health section in conjunction with the 1966 safety congress of the National Safety Council in San Francisco.

ACTION: Authority to conduct health section on 1966 California safety congress voted.

The commission further recommended that the Association work closely with the Nevada State Medical Association in the development of adequate health facilities in the Lake Tahoe area.

ACTION: Tenth District Councilor Yant requested to investigate the health care situation in the Lake Tahoe area and report to the Council.

23. *Scientific Board*

Councilor Shaw, chairman of the Scientific Board, presented a report containing both informational and action material. Actions were taken on the following:

(a) House of Delegates resolution #39-65 asked a Scientific Board study of hemodialysis centers, for which the board recommended formation of an ad hoc committee which would have access to authorities not members of the board.

ACTION: Scientific Board authorized to establish ad hoc committee for the study of hemodialysis centers.

(b) The board recommended adoption of a subcommittee report on medical libraries, which proposed that the Association contribute $1 per active member per year, to be divided between the Stanford Lane and the Los Angeles County Medical Association libraries and also that a technical committee consisting of named members be established to develop a technical program for comprehensive medical library service for members of the Association.

ACTION: Voted to refer subject of financial support of medical libraries to an ad hoc committee of the Council.

(c) The board recommended that the Association become a co-sponsor for a follow-up conference in California to the Second National Conference on Cardiovascular Diseases, that $800 be allocated to the support of the conference and that component societies be urged to participate and encourage attendance. A substitute motion which would have removed the Association from co-sponsorship and financial support was discussed but defeated by vote.

ACTION: Voted to co-sponsor follow-up conference in California to Second National Congress on Cardiovascular Disease, to contribute $800 toward the conference and to encourage component societies to encourage participation and attendance.

24. *Commission on Allied Health Services*

The chairman read a letter from a member in Napa County, in which complaint was made against radio announcements which were considered as over-commendatory to a professional group of lesser training than physicians.

ACTION: Letter referred to Commission on Allied Health Services.

Time and Place of Next Meeting

The chairman announced that the next meeting would be held at the Airport Marina Hotel, Los Angeles, on Saturday, August 7, 1965.

Adjournment

There being no further business to come before it, the meeting was adjourned at 4:35 p.m. in the memory of Doctors Junius B. Harris and William J. Kerr.

CARL E. ANDERSON, M.D., *Chairman*
MATTHEW N. HOSMER, M.D., *Secretary*

State Fee Schedules

Following is the report of the California Medical Association Ad Hoc Committee on State Fee Schedules:

Introduction

The 1964 House of Delegates adopted a Resolution which directed the Speaker to appoint this ad hoc Committee, and established its assignments and authority. In review, these were as follows:

That the Legislative and Executive branches of the State of California be immediately notified that:

(1) The *Schedule of Maximum Allowances for Medical and Related Services for the State of California* is not acceptable to the California Medical Association;

(2) The branches of the government of the State of California purchasing medical care should compensate physicians on the basis of the current *Relative Value Studies;*

(3) The fees paid by the State should reflect the usual and customary fees for medical services; and

(4) The Committee be empowered to negotiate with the appropriate State officials to achieve these goals.

The Committee held its first meeting in July of 1964 and since has held eight general meetings and four subcommittee meetings, where nearly 100 per cent attendance was maintained.

We invited as our guests the following representatives of the State government:

Mr. Leslie Waight, Medical Fee Analyst of the State Department of Finance, members of his Technical Advisory Committee and related State officials including Messrs. Carel Mulder, State Department of Social Welfare; Gene Zelle and Richard Young, M.D., of the Department of Vocational Rehabilitation; Charles R. Gardipee, Jr., M.D. of the Crippled Children Services, State Department of Public Health; Mr. Ed Beach, Chief of the Budget Division, State Department of Finance and Mr. Alan Post, Legislative Analyst.

We also had as our guests Mr. Ben Read and staff of the Public Health League; Dan O. Kilroy, M.D. and members of his Legislative Committee; Mr. Gene Potloff, Director of the California Physicians' Service Department of Research; and Doctors James C. Doyle, President, Ralph C. Teall, President-Elect and Carl E. Anderson, Chairman of the Council.

Conclusions and Recommendations

It is apparent that much of the year's activities of this Committee concerned the accumulation of data, opinions and experience. Certain improvements in the mechanism of the *Schedule of Maximum Allowances for Medical and Related Services for the State of California* seem quite possible and some hope of achieving proper representation on the Technical Advisory Committee of the Medical Fee Analyst seems appropriate. The recurrent frustrations involved in our efforts to achieve a more appropriate, higher level of fees and eventually a usual and customary fee system were neither new nor unexpected. Having experienced and evaluated their sources and causes, we are now in a position to present our interim conclusions and make recommendations for continuing efforts to achieve this major goal.

A review of the primary points covered in our discussions follows this section. Based on our discussions and conclusions, your ad hoc Committee recommends the following:

1. The CMA make known to the citizens of this State its position on medical care for all and its willingness to cooperate with all parties as spelled out in the 1964 House of Delegates Resolution No. 16-64.
2. The State Department of Finance be requested to accept and utilize in unabridged form, each current edition of the *Relative Value Studies* as the format for any system of payment.
3. The State Department of Finance be urged to accept the principle of variable conversion factors applied to separate sections of the *Relative Value Studies* when factors different from the statewide medians are used, and that monies now available to purchase medical care for recipients of State assistance be so applied to the current *Relative Value Studies.*
4. The State Department of Finance be urged to honor the concept that the State should purchase medical care for its recipients of State assistance on the same basis as is available to the public generally, and that, *as a step in this direction,* plans should be made to upgrade the level of fees paid to physicians to the level of the statewide median.
5. The State Department of Finance be urged to accept as its ultimate obligation the payment of usual and customary fees for professional services in accordance with the definition of usual and customary as adopted by the House of Delegates in 1964 (Resolution No. 21-64).
6. The Legislature, Department of Finance and State agencies be informed of the experience of the physician-sponsored prepaid medical care insurance program utilizing the usual and customary fee concept, and be urged to use similar insurance mechanisms in paying for medical care for recipients of State assistance when adequate funds become available to reflect the usual and customary fees.
7. The State Department of Finance be requested to have appointed to its Technical Advisory Committee to the Medical Fee Analyst, a minimum of four members selected from a list of names provided by CMA.
8. The CMA recognizes its responsibility to the people of California to (a) assist in the development and implementation of properly conceived and properly devised State medical care programs when the goal is to assure continuing high quality medical care to recipients of State assistance, and (b) to endorse and support those programs designed to assist those individuals in proven need of State assistance.
9. All State agencies administering medical care programs, the Department of Finance, and the Legislature be offered the continuing assistance of the Committee on Fees as consultants and advisors in all things pertaining or related to medical fees.
10. The Legislature be properly informed of our concern regarding quality, availability and economics of care being provided recipients of State assistance along with our appraisal of those factors causing breakdown in their programs, including recommendations for correction.
11. Full cooperation with the Legislature in studying these matters be authorized including use of statistical data available through present or past CMA studies when such data is essential to proper study and decision.
12. The Council be requested to instruct the Communications staff to make known the essence of this report and its recommendations to the membership in general by methods approved by this Committee.
13. Each member of CMA be advised of the progress made by this Committee and its predecessors, and determine for himself whether or not he wishes to participate in any of the State programs.
14. All Commissions and Committees of the Association be directed to adhere to these principles when approaching the State on matters of medical fees so that this House can be assured of continuity of these precepts.
15. This ad hoc Committee be continued, with instructions to press as hard as feasible in their negotiations for the acceptance of these recommendations by the appropriate State bodies.

Discussion

The early meetings were devoted to in-depth exploration of the designated functions and powers of the Committee and to the clear cut delineation of those CMA goals we were to implement. These goals were refined into their integral parts, and pro and con arguments surrounding them were explored. Even though the members of the Committee had been chosen for their previous experience in this field and even though the basic concepts were known, these deliberations proved the need for detailed discussion, careful planning, and careful coordination if the legitimate variations of viewpoint within the Committee, the activities of other CMA committees and the innumerable extrinsic factors were to be properly recognized and combined into an effective overall CMA plan of action.

It was immediately apparent that both our mandate from this House of Delegates and our own consensus demanded that our basic, constant long-range goal was to be the achievement of a system of payment of usual and customary fees for services provided by the physicians of California to recipients of State assistance. This system seeks to assure the care of these patients in the mainstream of high quality medical care side by side with our other patients for fees equal to those usually charged by the treating physician, recognizing, the legitimate variations in fees customary in the community in which the services are rendered. This goal specifically denies the propriety of any single, rigid schedule of fees at any level, including statewide or even regional median levels.

The second obvious goal was the use of the unadulterated, unabridged, current CMA Relative Value Studies as the basis for any system of payment and communication used by the State in these programs. Establishment of the *RVS* as the basic mechanism would assure equitable distribution of whatever funds were available during the interval period necessary to the development of the usual and customary fee system. In addition, a seldom emphasized but important benefit arising from use of the *RVS* would be its advantages as a means of communication of the nature and method of treatment involved. The broad scope of the listings, the nomenclature, the detailed definition of services and the ground rules of the *RVS* have been developed by physicians to describe services physicians provide. Establishment of the unabridged *RVS* as the basic mechanism would provide a proper and uniform means of communication between physicians and the State agencies even after a single fee schedule was discarded in favor of the usual and customary fee system. And, finally, the *RVS* would provide an underwriting mechanism of proven worth through which the State could determine its budgetary needs.

A subsidiary point of agreement in our early deliberations covering the use of the *RVS,* concerns the need for variable dollar conversion factors for each of the sections of the *RVS* when any but the statewide median conversion factors are used. This technical point deserves considerable attention in the interest of equity between physicians so long as the State insists on a rigid fee schedule, particularly a substandard rigid fee schedule such as is presently used.

There was general and ready agreement as to the above three points (usual and customary fees, *RVS* as the basis of payment and variable dollar conversion factors). Initially, there was considerable divergence of opinion as to the methods and sequences to be employed in the achievement of these goals. As our meetings widened to include various involved State officials, these divergencies tended to narrow. Under the pressures of hard facts of State administrative philosophies, budgetary limitations and expectations, it became clear that although certain accommodations were inevitable, a unified front in all approaches to the State on these matters was essential in achieving final success. It also became clear that success would come slowly and in steps rather than through one bold stroke.

The first meeting with the State agency personnel included the Medical Fee Analyst and his Technical Advisory Committee made up of various medical administrators from the agencies. These are the administrators responsible for the development of the present *Schedule of Maximum Allowances for Medical and Related Services for the State of California,* and the ones with whom the previous ad hoc Committee of the CMA Council had dealt. The discussions were frank and productive.

The Medical Fee Analyst outlined his duties, prerogatives and limitations. It is important that members of the medical profession fully realize that the State administrators cannot negotiate. They come only to seek information and advice in their attempt to devise systems which will evoke sufficient cooperation from the medical profession to accomplish the purposes of the programs as they see them. They attempt to reconcile these findings with the mandate and budgets provided by the Legislature and the pressures exerted by individual legislators. Further, it would be safe to say that, in spite of the negotiating role provided this ad hoc Committee by the House of

Delegates, the Committee actually lacks all of the tools of negotiation since it cannot, nor does it desire to, enforce its decisions on either the constituent societies or the individual members of CMA. It is obvious that under these circumstances, any conclusions or understandings reached between representatives of the State and your representatives have neither the aura nor the power of negotiated commitment. The State will make the final decisions and the State is free to change these decisions at will. When its decisions are incompatible with our goals, our only recourse is public exposure of the inadequacies and dangers of the system devised.

Your representatives in these discussions have but two sources of power. The first is, of course, the support and persuasive power of the CMA with its constitutent societies and its members. The second is the presentation of such clear-cut, unassailable and consistent arguments in support of our contentions that those making decisions at all levels of the State government will recognize the need to consider and include our recommendations in their planning if their programs are to achieve the medical goals we all seek.

Over and over the point was made that in the final analysis, the medical success of the State medical care programs can come only through physicians. The programs can provide funds, but cannot provide services. It is clear that the Legislative intent is to make available to recipients of State assistance the same high quality of medical care that is available to all California residents and it is the administrators' responsibility to provide an environment in which physicians can accomplish this common purpose. It is our contention that increasing administrative demands, the *Schedule of Maximum Allowances for Medical and Related Services for the State of California* and the low level of fees, are adversely affecting physician participation in these programs. Whenever and wherever State administrative decisions discourage physician participation in the programs, the quality and availability of medical care are seriously affected.

These theses were supported by a thorough discussion of the purposes, methods and general acceptance of the *RVS* by physicians and other private and public administrators. State administrators expressed the opinion that they have done a good, if not absolutely complete job of basing their schedule on the 1960 *RVS*. They felt that the changes they have made were not only minor but were essential for administrative purposes because of budgetary limitations. Their lack of detailed knowledge in the field in which they were making the final decisions is epitomized by the amazement expressed when it was pointed out that the *Schedule of Maximum Allowances for Medical and Related Services for the State of California* includes well over 700 changes in nomenclature, ground rules and values from the *1960 Relative Value Studies.* These changes are so significant as to seriously impair the usefulness of their efforts. It was pointed out also that CPS and others have found it possible to administer prepaid programs based on the unadulterated *RVS* even though some change in the previous administrative methods were required to accomplish this purpose. It was made clear that even though budgetary limits were recognized, the method employed to reconcile these to the *RVS* by the Technical Advisory Committee had been incorrect and completely destroyed relativity in large sections of the *RVS*. The need for variable conversion factors in their substandard schedule was emphasized. The placing of arbitrary values on over 100 "by report" items was decried.

These exchanges appeared to produce some real hope of developing a revision of the *Schedule of Maximum Allowances for Medical and Related Services for the State of California* to follow more closely the 1960 *RVS*. Such revision is to be accomplished through consultation with the Committee on Fees of the CMA. An effort is to be made to adapt the legitimate needs of the State to the *RVS* without destroying its basic precepts. Because of the usual inertia surrounding such administrative changes by State agencies as well as their preoccupation with the current legislative session, these consultations are still in the planning stage. However, in view of the expressed desire of the Medical Fee Analyst to use CMA help and to achieve an accurate reflection of the *RVS* in the *Schedule of Maximum Allowances,* cautious optimism that the mechanism of determining the nature and method of services and retaining the relative value of these services will be improved eventually, seems in order.

Representatives of various State agencies administering funds for medical care programs were interviewed. Of greatest significance was the presentation by the representative of the State Department of Social Welfare who stated unequivocally that it was the firm belief and policy of his Department that the level of payments for physicians' services under these programs should quite properly be placed at a level below normal fees and that approximately 80 per cent of normal was the presently accepted level. He expounded the well-known arguments of indigency, reduced payments for low-income CPS policies including State employee programs, CMA-implied acceptance of this level during the 1957 consultations and the general acceptance implied by the participation in these programs of large numbers of California physicians. Others expressed the belief that the physicians had a responsibility to service these programs regardless of the fee schedule or the regulations. The many and compelling arguments in opposition to these beliefs were presented with all the clarity and force available. The persistence and force of these administrative philosophies is pointed up by the similar testimony subsequently presented to a Senate committee by the same official and the statements of other State administrators at all levels. This firm commitment at the administrative level in all State agencies to reduced fees for the care of recipients of State assistance constitutes *the major obstacle* to achieving the usual and customary fee system.

At this meeting and subsequently, the entire mechanism of the usual and customary fee system was presented in detail to the State administrators. The medical need for retaining these patients in the mainstream of quality medical care, the normal and proper variations in fees charged within a given community and in various areas of the State, the importance of maximum physician participation, the dangers of backwash medical care and other factors involved, were all presented and tied into the concept of usual and customary fees. The State officials countered with claims of administrative complexities and the high and uncertain costs of such a system. It was obvious that administrative philosophies firmly adhered to a single, rigid fee schedule and that thoughts of departure from such single, rigid fee schedule and that thoughts of departure from such a system raised spectres of chaos in their minds. At this point, the Committee offered in exchange for provision of the usual and customary fee system to exert the full persuasive powers of the CMA to make available to the agencies the services of various review committees of the constituent county societies, and if necessary, CMA committees, to assist in making the system successful. It was pointed out that pilot programs in three areas have indicated that such a system would encourage physician cooperation to a maximum degree so that the need for the policing mechanisms so much a part of the agency thinking, would be minimal, leaving any residual problems to be adjudicated by existing and active medical society committees. The importance of such cooperation to the success of the system was emphasized. The resultant improvement in the programs themselves seemed axiomatic.

One budgetary problem raised concerned the determination of the funds needed to cover medical costs when no fixed schedule of fees can be used as the basis for budgetary estimates. The argument was advanced by us that if enough funds were available to pay a rigid fee schedule at the median level of fees, it would be actuarially possible to ignore this fixed schedule and pay the usual and customary fees since the properly determined median, by its very nature, includes these variations. Until adequate funds are made available for this level of payment, if only for a pilot study, it would be difficult to convince the agency officials on this point. Presently CPS is experimenting in this area. The Santa Barbara Plan suggests the feasibility of this actuarial approach even though this program pays at a lower level. But to repeat, until funds are available to pay the median levels, the usual and customary fees cannot be seriously considered.

In actual practice the agencies set up budgets based on a predetermined fee schedule and ask the Legislature to provide the funds to cover the aggregate of services they expect to purchase. Under the present system and in terms of Parkinson's law, any budgetary increases are usually for added services and departmental expansions, not for increased fees for services purchased. A raise in the level of fees would ordinarily require agency initiation as well as Legislative approval. Since the agencies are convinced that the present level of fees is proper, they are not likely to initiate a proposal for a higher level of fees.

Therefore, it is obvious that under existing conditions our hopes for initiation of budgets sufficient to include usual and customary fees cannot rest on agency cooperation and must rest on Legislative directives.

The possibility of covering all of the programs through the insurance mechanism was presented and discussed. The advantages to both sides are important and this method must be considered in focus with other goals. However, when pressing for the insurance principle, we should stay within the concept of usual and customary fees, specifically avoiding any commitment to a substandard level of fees or a concept of fixed fee schedules, both of which this Committee is working to eliminate.

Later consultation was held with the Director of the Budget and the Legislative Analyst. The various points made to the lower echelon officials were re-emphasized and the possibilities of larger budgets necessary to obtain usual and customary fees were explored. Again, the discussions were frank and friendly, but little concrete hope of increases from the present composite $3.87 conversion factor level could be developed. It became increasingly evident from this meeting that any hope of establishing the basic principle of usual and customary fees for physician services and funds to accomplish this purpose lay with initiation by the Legislature. The administrators appeared willing to improve the mechanism of payment but were not motivated to seek a higher level of fees.

One encouraging development from this meeting was the agreement that the medical profession should be represented by practicing physicians on the Technical Advisory Committee to the Medical Fee Analyst so that the Analyst, in whose hands the final recommendations must lie, would have advice from both the administrators and those who must provide the services to be payed for. It appears that this change will occur. If such CMA representatives are chosen for their technical knowledge in the area of fee schedules and in the area of fee payments and administration, this type of representation at the basic level can do much to improve the mechanism of payment, if not the level of payment.

With the development of the conclusion that any hope of achieving a higher level of fees and eventually usual and customary fees lies with the Legislature and not with the administrators, a meeting was arranged with the Legislative Committee of the CMA. It was soon obvious that in the opinion of the Legislative Committee, there was no hope at this Legislative session of passage of Senate Bill No. 374, which had been introduced at the request of the CMA and which sought to amend the present legislation to include a doctrine of fees for physicians' services "commensurate with and as nearly as possible equal to the usual and customary amounts paid for such services by the public generally." In a Legislature preoccupied with the compelling problem of reapportionment, raising taxes and lowering budgets, a request for more money, no matter how justified, seemed doomed to fall on deaf ears at this time. Nevertheless, we must marshall all of our data and all of our resources for Legislative presentation at the appropriate time and in the appropriate places if we are to hope to accomplish this fundamental goal.

This Committee is grateful for the willing participation of our guests in the discussions of our problems. We are deeply indebted to the members of the CMA staff who have provided data, information and secretarial service to the Committee. The Chairman would like to thank each member of this Committee for his dedicated and thoughtful participation.

Respectfully submitted,

Joseph Boyle, M.D.
Vincent P. Carroll, M.D.
M. S. Futterman, M.D.
H. Dean Hoskins, M.D.
Arthur F. Howard, M.D.
Robert B. Olney, M.D.
Glenn A. Pope, M.D.
Maurice Salomon, M.D.
Samuel R. Sherman, M.D.
A. B. Sirbu, M.D.
Robert Watson, Jr., M.D.
Roger C. Isenhour, M.D.,
Chairman

In Memoriam

Dill, Joseph N., Crockett. Died June 18, 1965, in Pinole, aged 44. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1953. Licensed in California in 1954. Doctor Dill was a member of the Alameda-Contra Costa Medical Association.

◆

Folkins, Frank H., Redlands. Died June 16, 1965, in Riverside, aged 81. Graduate of State University of Iowa College of Homeopathic Medicine, Iowa City, 1910. Licensed in California in 1911. Doctor Folkins was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

◆

Gehrand, Henry C., Sierra Madre. Died June 4, 1965, in Sierre Madre, aged 64. Graduate of Washington University School of Medicine, St. Louis, Missouri, 1937. Licensed in California in 1942. Doctor Gehrand was a member of the Los Angeles County Medical Association.

◆

Goldberg, Benjamin, Palm Springs. Died July 9, 1965, in Palm Springs, aged 72. Graduate of the University of Illinois College of Medicine, Chicago, 1916. Licensed in California in 1943. Doctor Goldberg was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Hamilton, John B., Glendale. Died June 13, 1965, in Glendale, aged 62, of carcinoma of lung. Graduate of the University of Virginia School of Medicine, Charlottesville, 1937. Licensed in California in 1946. Doctor Hamilton was a member of the Los Angeles County Medical Association.

◆

Hanssen, Egil, Glendale. Died June 19, 1965, in Portland, Oregon, aged 66, of a coronary. Graduate of the University of Minnesota Medical School, Minneapolis, 1934. Licensed in California in 1939. Doctor Hanssen was a member of the Los Angeles County Medical Association.

◆

Harrison, William Justin, Cathedral City. Died May 31, 1965, aged 70. Graduate of Chicago College of Medicine and Surgery, Illinois, 1916. Licensed in California in 1927. Doctor Harrison was a retired member of the Riverside County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Hilliard, John William, Pomona. Died May 23, 1965, in Pomona, aged 51, of cancer. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1942. Licensed in California in 1942. Doctor Hilliard was a member of the Los Angeles County Medical Association.

◆

Kerr, William John, Blue Lake. Died June 10, 1965, in Eureka, aged 76, of heart disease. Graduate of Harvard Medical School, Boston, Massachusetts, 1915. Licensed in California in 1917. Doctor Kerr was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

◆

Lennon, Milton B., San Francisco. Died July 7, 1965, in San Francisco, aged 87. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1901. Licensed in California in 1901. Doctor Lennon was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

◆

Miller, Rudolph Howard II, Oakland. Died June 18, 1965, in Palo Alto, aged 42, of primary myocardial disease. Graduate of Howard University College of Medicine, Washington, D.C., 1947. Licensed in California in 1954. Doctor Miller was a member of the Alameda-Contra Costa Medical Association.

◆

Montgomery, William Orrie, San Francisco. Died July 2, 1965, in San Francisco, aged 82. Graduate of Cooper Medical College, San Francisco, 1907. Licensed in California in 1907. Doctor Montgomery was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

◆

Nelson, Charles Frederick, Beverly Hills. Died June 15, 1965, in Los Angeles, aged 80, of pneumonia. Graduate of Rush Medical College, Chicago, Illinois, 1911. Licensed in California in 1911. Doctor Nelson was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Osborn, Harold Blackman, Fillmore. Died May 30, 1965, aged 81. Graduate of Columbia University College of Physicians and Surgeons, New York, New York, 1911. Licensed in California in 1912. Doctor Osborn was a member of the Ventura County Medical Society, a life member of the California Medical Association, and a member of the American Medical Association.

◆

Parkinson, Harold Obediah, San Francisco. Died July 7, 1965, in San Francisco, aged 64. Graduate of the

University of Edinburgh Faculty of Medicine, Edinburgh, Scotland, 1930. Licensed in California in 1931. Doctor Parkinson was a member of the San Francisco Medical Society.

✣

RUSKIN, ISIDORE WILSON, Los Angeles. Died July 9, 1965, in Los Angeles, aged 68, of circulatory disease. Graduate of the University of Toronto Faculty of Medicine, Ontario, Canada, 1921. Licensed in California in 1947. Doctor Ruskin was a member of the Los Angeles County Medical Association.

✣

SARVIS, MARY ALICE, Berkeley. Died June 16, 1965, in Oakland, aged 50. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1942. Licensed in California in 1944. Doctor Sarvis was a member of the Alameda-Contra Costa Medical Association.

✣

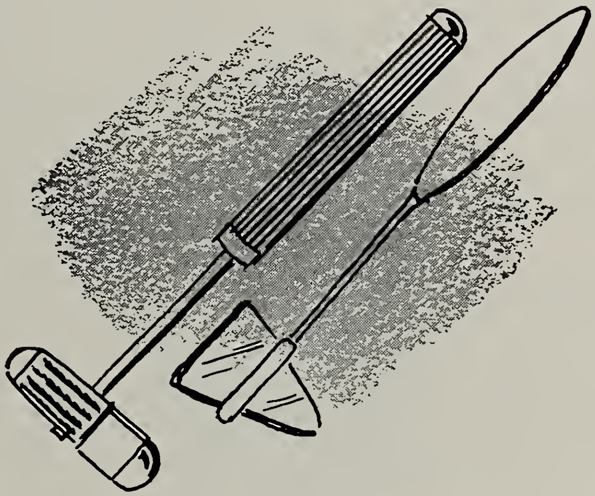
SLOCKBOWER, EDITH TREPTOW, Los Angeles. Died June 3, 1965, in Los Angeles, aged 43. Graduate of State University of Iowa College of Medicine, Iowa City, 1945. Licensed in California in 1954. Doctor Slockbower was a member of the Los Angeles County Medical Association.

✣

STAFFORD, HENRY EDWIN, Glen Ellen. Died April 30, 1965, in Sonoma, aged 67. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1922. Licensed in California in 1922. Doctor Stafford was an associate member of the Sonoma County Medical Society.

✣

THOMPSON, ROBERT P., San Francisco. Died June 26, 1965, in San Francisco, aged 51, of anuria following surgery. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1941. Licensed in California in 1941. Doctor Thompson was a member of the San Francisco Medical Society.



PUBLIC HEALTH REPORT

MALCOLM H. MERRILL, M.D., M.P.H.
Director, State Department of Public Health

IN MID-MAY the biggest outbreak of a water-borne disease in modern California history occurred in the City of Riverside. A conservative estimate is that 18,000 residents of this southern California community and its environs were stricken in some degree by *Salmonella typhimurium* as a result of an as yet undertermined contamination of the city's municipal water system.

The epidemic began about May 18 and soared to its peak by the 27th. The last such water-borne epidemic of any size was in 1938 in Rochester, New York. The cause of that episode, in which approximately 32,000 persons became ill, was never determined. The last such epidemic in California was one of typhoid fever in Santa Ana in 1925.

The Riverside County Health Department became aware of the epidemic May 24 when physicians reported seeing unusually large numbers of patients with acute gastroenteritis. The State Health Department was notified May 27. By that time more than 1,000 persons were ill and *Salmonella typhimurium* had been detected by laboratory examination of stools.

A state-federal team of epidemiologists, sanitary engineers, nurses and laboratory workers was in Riverside the following day to assist the local health department staff in defining and controlling the epidemic. After food products had been eliminated as the cause of the infection, attention focused upon the city's water supply, particularly in the light of the rising numbers of ill persons and the broad geographic spread of the cases.

On June 2 a presumptive positive isolation of *Salmonella typhimurium* was obtained from a sample of water from the distribution system, and chlorination of the water supply was begun. Before that date, 75 additional samples had been collected. Subsequently, samples from five locations in the city proved positive.

In the epidemiologic investigation, data were obtained by phone surveys and personal visits to physicians, hospitals, pharmacists and a representative sample of the total city population reached through a household survey. Information was collected from a random sample of 1,500 households (5,000 people) in the city and approximately 350 households (1,000 people) in contiguous areas not on the city water system.

On the basis of these data it is estimated about 13 per cent, or 14,000, of the 110,000 residents of Riverside, were sick; that there was an additional 2,000 cases in people living in nearby areas who work in the city, and that about 2,000 secondary cases occurred, for a total of 18,000 persons who have been ill.

In general the illness has been mild, with fewer than a hundred persons admitted to hospital. In some children the illness was characterized by diarrhea and fever of 102 to 103°F. In both children and adults the duration of the illness varied with the severity. Mostly it was of short duration, but some cases lasted ten days or longer. Three patients have died, a six-day-old infant, a teen-age girl and a woman in her fifties. The latter however, had underlying disease. The number of cases is now declining and it appears prevention methods are successfully checking the disease.

Current team efforts emphasize measures to minimize the hazard of secondary spread and to determine the source of contamination of the city water supply. Since infants and the aged or debilitated are particularly vulnerable to this disease, the health department team is working with hospitals and nursing homes and special precautionary measures are being taken. Restaurant operators in the city and the general public have been alerted and advised on special precautions.

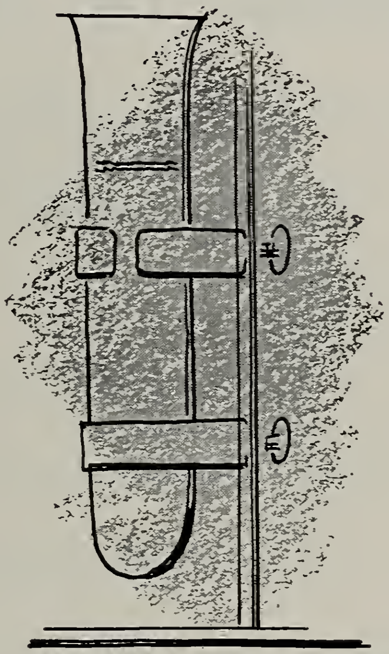
An intensive investigation is under way to determine the source of contamination. The water system consists of a series of 35 deep wells both in and outside the city. The distribution system comprises some 800 miles of pipeline serving 110,000 people. Because of the purity of the water it has never been chlorinated.

Regular monitoring of the water supply by standard coliform counting techniques before and even during the epidemic did not reveal coliform organisms in excess of acceptable numbers. Nevertheless, as was previously mentioned, water samples obtained from five locations were shown to contain *Salmonella typhimurium*. The geographic distribution of cases corresponds with that of the city water supply.

As this is written engineers are backtracking through the distribution system, seeking the source of contamination. System repair work has been checked, the possibility of contamination from animal life has been ruled out, and system leaks are being investigated along with the land use above the lines.

The state-federal team completed its field epidemiologic surveys and water system checks the end of June, when it moved out of Riverside. Now begins the arduous chore of winnowing a prodigious amount of field reports and survey results, coupled with a recapitulation of water system investigations in an endeavor to determine the source of contamination.

The State Health Department will continue to work with its local counterpart in efforts to solve this perplexing episode.



CALIFORNIA MEDICAL ASSOCIATION

1966 ANNUAL SCIENTIFIC ASSEMBLY

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PLANS FOR THE 1966 ANNUAL SCIENTIFIC ASSEMBLY ARE NOW IN PROGRESS

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LETTERS *to the Editor*

Community Organization to Help the Handicapped—A Guide

THERE IS INCREASED public awareness and concern for the poor, the deprived, the unwanted, the retarded and the physically handicapped. This, coupled with the allotment of funds from State and Federal sources for Aid to Communities, calls for coordinated planning at local levels.

Experience gained in the Child Development Center at Children's Hospital in San Francisco is presented here as a guide for those who may be initiating such service.

The focus must always be on the child, his family and their needs. The focus must not be deflected to organizations, agencies or staff personnel.

Local experienced people whenever possible should be enlisted in the planning. All existing facilities and agencies in the community should be fully utilized, adapted and expanded rather than creating new organizations. New organizations call for additional superstructure and increased expenditure which leeches the funds without bringing necessary aid to those who need it.

The basic needs of deprived, retarded or handicapped children are the basic needs of all children, namely a home and the love and security that goes with it, medical care, education, training for employment in adult life, recreation and the right to worship.

Homes: In infancy and early childhood there is no perfect substitute for the child's own home and his own parents. This is the age during which the child learns trust, love, truth, right and wrong, the role of parents and siblings. If there is no home or parents the next best substitute is a good foster home.

After the age of seven or eight years the child becomes more involved with his peers. At that age, therefore, separation is better tolerated. If a child has a severe handicap such as deafness, blindness, cerebral palsy, or spina-bifida, or a combination of these a special class or a boarding school for five days a week may be necessary. The weekends, holidays and vacations should be spent at home.

The child who is severely handicapped often both physically and mentally may need a semi-hospital situation during much of his childhood. He may need nursing care as well as rehabilitation services and this often cannot be adequately provided in a home situation with ambulatory care.

After the school years the adult with a severe handicap will need living arrangements especially adapted for his needs such as entrance without stairs, elevators with doors wide enough to accommodate a wheelchair, ramps, personnel in the building trained to assist, and transportation.

Medical Care: Medical care is the service now most adequately provided to handicapped children. In addition to private care, there are hospital and university medical clinics, rehabilitation services and Crippled Children Services available for a wide category of diseases. Unfortunately total evaluation of the child not only medically but also psychologically and educationally is not always available in medical centers. A Child Development Center in which such comprehensive evaluation is possible should be available to all practicing physicians.

Education and Training: The public school provides many services for handicapped children. There are now classes for both the trainable and educable children, there are special provisions for the deaf, blind, the neurologically handicapped, the emotionally disturbed and the physically handicapped. Even with this impressive array of services there are large gaps. The public school does not provide facilities for the pre-nursery and nursery school child who is deaf, blind, retarded, aphasic or who has multiple handicaps. Recent studies indicate that 50 per cent of intellectual growth takes place by four years of age and 80 per cent by eight years of age. Provision for this education should be assumed by the voluntary agencies until such a time as public funds are available.

There are some specialized State schools but these also tend to take only the so-called "normal" deaf, blind or aphasic children.

The larger communities may have sheltered workshops for older handicapped children and adults.

Experimentation with work areas in small industries should be explored.

Employment of the handicapped needs to be kept under constant surveillance. In Sydney, Australia the Spastic Society purchased a plant that manufactured electronic equipment and the entire factory is now run by spastic individuals.

Recreation: Recreation for the handicapped has been almost entirely neglected. This may be the easiest activity to initiate. Recreation can serve children who have a variety of problems. Various agencies can be persuaded to participate in the program both with funds and with volunteers.

There is available an excellent book which describes in detail the methods for instituting a recreation program, namely "Recreation for the Physically Handicapped" by Janet Pomeroy, Macmillan & Co.

Worship: The churches and synagogues should be sensitive to many needs of handicapped children and their families. There are some church-supported homes for the retarded but there should be many more. Very few churches have adapted their religious instruction to suit the handicapped whether he be deaf, blind or retarded.

The church building is often vacant most of the week and the space for some of the above described activities could be granted.

Method of Procedure: It is necessary that someone take the initiative in organizing a community for action. In the case of the handicapped child the most appropriate and logical person to assume leadership is the physician. Such a child is usually under close medical supervision all of his life—no other discipline or individual has this type of long-term contact with the child. The move therefore to organize the community might start in the County Medical Society or in the Pediatric Society, it might be instigated by the Public Health Department.

The existing community services should be listed and participation invited. Representatives from the medical community should meet with local leaders in public health, welfare, education, religion, recreation and so forth several times for open discussion and clarification of roles. Outside experts in various fields might be invited to participate such as from Public Health Services, Crippled Children Services, Centers concerned with child development, educational centers and so forth.

After a few general sessions for organization and clarification smaller committees should be formed to pursue special needs. *If discussion continues without action for a prolonged period there may never be any action.* This is particularly true if the group first resorts to applying for Grants and waiting for financial aid. Grants can be a delusion. If a Grant is obtained the usual procedure is first to hire a director and secretarial help and rent office space, a second step is to make an elaborate survey and then the third step is to reapply for the Grant because the original one is nearly exhausted. It is better to start an active vigorous program that is woven into the existing fabric of the community. Local sources can be tapped for financial aid and when the needs are clear outside funds can be sought.

The logical subdivisions for action are:

1. Nursery schools and pre-nursery schools
2. Day Care homes
3. Counseling
4. Recreation
5. Church activity
6. Parents groups
7. Legal rights and benefits
8. Transportation
9. Employment; including vocational testing, guidance, training and placement
10. Comprehensive diagnostic and rehabilitation services.

H. E. THELANDER, M.D., *Medical Director*
Child Development Center, Children's Hospital,
3700 California Street, San Francisco,
California 94118

NEWS & NOTES

NATIONAL • STATE • COUNTY

STATE FEE SCHEDULES

See report of the California Medical Association Ad Hoc Committee on State Fee Schedules, beginning on page 142, this issue of CALIFORNIA MEDICINE.

ALAMEDA

Dr. Wayne P. Chesbro, Berkeley, has been honored by the United States Public Health Service for his leadership in the National Disaster Preparedness program.

A member of the American Medical Association's Committee on Disaster Medical Care and chairman of the California Medical Association's Committee on Disaster Medical Care, Dr. Chesbro has devoted years to developing an effective nationwide program for survival in both war and peacetime emergencies.

He received a plaque from Dr. Luther L. Terry, U.S. Surgeon General, at the time of the American Medical Association meeting in New York in June.

* * *

An infectious disease seminar wil be held at Children's Hospital Medical Center of Northern California, Oakland, on Saturday, October 9.

Speakers for the seminar will be Dr. Henry Kempe, professor and chairman of the department of pediatrics, University of Colorado Medical Center; Dr. Paul Wehrle, chief, communicable disease division, Los Angeles County General Hospital; Dr. Moses Grossman, professor of pediatrics, assistant dean of the University of California School of Medicine in San Francisco; and Dr. Henry B. Bruyn, director of Cowell Memorial Hospital, University of California, and associate professor of medicine and pediatrics at the University of California School of Medicine.

The fee, including luncheon, will be $10. Reservations may be made by writing Medical Staff, Children's Hospital Medical Center, 51st and Grove Streets, Oakland, California 94609.

LOS ANGELES

The 1965-66 officers of the **Los Angeles Radiological Society,** elected in June and to take office in September and serve until September, 1966, are: President, Dr. Chester P. Bonoff; vice-president, Dr. Victor G. Mikity; treasurer, Dr. Austin R. Wilson; secretary, Dr. Joseph A. Parks.

* * *

Dr. A. William Liley of New Zealand will address a special invitational dinner meeting at Memorial Hospital of Long Beach Tuesday evening, August 31. He will discuss **prenatal transfusion** to prevent intrauterine death from erythroblastosis, a procedure he pioneered.

Dr. Liley is senior research fellow and a diplomate in obstetrics at the University of Auckland and directs the antenatal clinic in Auckland's National Women's Hospital. He has been in this country doing research at Columbia-Presbyterian Medical Center, New York.

Further information may be obtained from Dr. Elmer R. Jennings, Director of Laboratories, Memorial Hospital of Long Beach.

GENERAL

The American Academy of Pediatrics will hold its 34th annual meeting October 23-28 at the Palmer House, Chicago.

General session panels and symposiums will deal with carbohydrate metabolism; teenagers; recent epidemics (including encephalitis and rubella); bases of child development; recent developments in pediatrics and antimicrobial agents.

Several special reports will be given, including one on the Food and Drug Administration by Joseph F. Sadusk, Jr., M.D., director of the FDA.

* * *

The Pacific Coast Oto-Ophthalmological Society will hold its annual meeting at the Broadmoor Hotel, Colorado, May 8-13, 1966. Further information may be obtained from George E. Morgan, M.D., Executive Secretary-Treasurer, Pacific Coast Oto-Ophthalmological Society, 3242 West 8th Street, Los Angeles, California, 90005.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts
for Postgraduate Course Information

CMA:	**California Medical Association** For information regarding Postgraduate Institutes and Circuit Courses, Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. PRospect 6-9400, Ext. 68.
LLU:	**Loma Linda University** For information on courses contact: W. F. Norwood, Ph.D., Assistant Dean and Chairman, Division of Continuing Education, Loma Linda University School of Medicine, 1720 Brooklyn Ave., Los Angeles, California 90033, ANgeles 9-7241, Ext. 214.
PRES. MED. CTR.	**Presbyterian Medical Center** For information on courses contact: Arthur Selzer, M.D., chairman, Education Committee, Presbyterian Medical Center, Clay and Webster Streets, San Francisco 94115. WEst 1-8000.
UCLA:	**University of California at Los Angeles** For information on courses for physicians or ancillary personnel contact: Thomas H. Sternberg, M.D., Assistant Dean and Head, Continuing Education, U.C.L.A. Medical Center, Los Angeles, 90024, 478-9711, Ext. 2114.
UCSF:	**University of California, San Francisco** For information on courses for physicians or ancillary personnel contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, University of California Medical Center, Room 565-U, San Francisco 94122, 666-1692.
USC:	**University of Southern California** For information on courses contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, USC School of Medicine, 2025 Zonal Ave., Los Angeles 90033, CApital 5-1511, Ext. 300.
STAN:	**Stanford University** For information on courses for physicians or ancillary personnel contact: Roy Cohn, M.D., Associate Dean for Graduate Affairs, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto, DAvenport 1-1200.

*Fee to be announced. †Hours to be announced.

AUGUST

August 18-22—**Advanced Seminars in Urology.** UCLA at Lake Arrowhead Conference Center. Wednesday-Sunday. 18 hours. $110.

August 21-22—**Infertility.** UCLA. Saturday-Sunday. 14 hours. $60.

August 30-September 2—**American Hospital Association.** San Francisco. Monday-Thursday. Contact: Edwin L. Crosby, M.D., director, 840 North Lake Shore Drive, Chicago 11, Illinois.

SEPTEMBER

September 2-April 14—**Stockton Postgraduate Study Club.** 1 Thursday a month: 9/2, 10/14, 11/4, 12/9, 1/6, 2/10, 3/3, 4/14. 16 hours. Contact: San Joaquin County Medical Society, P.O. Box 230, Stockton.

September 9-11—**Saint John's Hospital Annual Postgraduate Assembly.** Thursday-Saturday. Contact: John C. Eagan, M.D., director, 1328 Twenty-second Street, Santa Monica.

September 13-19—**Pediatric Allergies.** UCSF. Monday-Sunday.*†

September 14-November 30—**Medical Radio Conferences.** UCSF. Tuesdays.

September 15-16—**Los Angeles Pediatric Society Annual Brennemann Memorial Lectures.** International Hotel, Los Angeles. Wednesday-Thursday. 9/15: 4:00 p.m. to 10:00 p.m., 9/16: 9:00 a.m. to 4:30 p.m.

September 16-December 9—**Medical Radio Conferences.** UCSF. Thursdays.

September 16-18—**Western Section, Association for Research in Ophthalmology Meeting.** Tahoe Alumni Center, Lake Tahoe (North Shore). Thursday-Saturday. Contact: Daniel G. Vaughan, M.D., University of California Medical Center, San Francisco 94122.

September 16-May 19—**Postgraduate Medical Lecture Series.** UCLA in San Bernardino and Riverside Counties. 3rd Thursday of each month. 18 hours. No fee.

September 18—**Cardiovascular Disease Symposium.** Jointly sponsored by Santa Barbara and Ventura Counties Heart Associations. Santa Barbara Biltmore Hotel. Saturday from 9:00 a.m. to 5:00 p.m. Contact: Wendell D. Klossner, M.D., chairman, Santa Barbara County Heart Association Symposium Committee, 1478 E. Valley Rd., Santa Barbara.

September 20-23—**Recent Advances in Internal Medicine.** UCSF. Monday-Thursday.*†

September 20-October 13—**Sacramento Valley Circuit Courses** presented by CMA in cooperation with UCSF. Dunsmuir: Mondays, Chico: Tuesdays, Auburn: Wednesdays. $30.: Spring and Fall. Spring Courses: February 21-March 16, 1966.

September 21-October 26—**Specific Syndromes Associated with Mental Retardation.** UCSF at Sonoma State Hospital, Eldridge. Tuesdays.*†

September 22-December 15—**Psychotherapeutic Medicine for Non-Psychiatrists.** UCSF. Wednesdays.*†

September 23-October 28—**Preventive Psychiatry.** UCSF at Modesto State Hospital, Modesto. Thursdays.*†

September 25-26—**Child Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.*†

September 25-26—**Manifestations and Therapy of Anxiety.** UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday.*†

September 28—**American Academy of Pediatrics, California Section III, Annual Seminar on Epilepsy.** Town and Country Hotel, San Diego. Tuesday. 4 hours. $10. Contact: J. Richard Hill, M.D., 525 Hawthorn Street, San Diego.

September 29-30—**Los Angeles County Heart Association Annual Fall Symposium on Cardiovascular Disease.** Statler Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hours. Contact: Harold Miller, M.D., chairman, Professional Education Committee, 2405 West Eighth Street, Los Angeles 90057.

September 29-October 1—**San Francisco Heart Association Annual Postgraduate Symposium on Heart Disease.** St. Francis Hotel, San Francisco. Wednesday-Friday. 18 hours. Contact: Mrs. Frances MacKinnon, 259 Geary Street, San Francisco.

OCTOBER

October 1-2—**San Diego County Heart Association Annual Professional Symposium on Heart Disease.** Town and Country Hotel, San Diego. Friday-Saturday. 8 hours. Contact: James E. Lasry, M.D., chairman, Professional Education Committee, 3545 4th Avenue, San Diego 92103.

October 1-2—**Urology.** UCSF. Friday-Saturday.*†

October 5-November 30—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesdays.*†

October 7-9—**Obstetrics and Gynecology.** UCSF. Thursday-Saturday.*†

October 8-9—**Western Industrial Medical Association.** Hilton Hotel, San Francisco. Friday-Saturday. Contact: Christine Einert, M.D., 629 Euclid Avenue, Berkeley 94708.

October 9—**Immunological Disease and Infectious Disease in Children.** Children's Hospital Medical Center, 51st and Grove Streets, Oakland. Saturday. 7 hours. Contact: Children's Hospital Medical Center.

October 9-10—**Cytology for Pathologists.** UCSF. Saturday-Sunday.*†

October 12—**Northeastern California Rheumatoid Foundation Seminar: Medical and Surgical Aspects of Arthritis.** Mercy Hospital, Sacramento, Tuesday. Contact: Harold B. Strauch, M.D., 4101 J Street, Sacramento.

October 12-November 16—**Neuropsychiatry in Daily Practice.** UCSF at Agnews State Hospital, San Jose. Tuesdays.*†

October 15-16—**Central Nervous System Infections.** UCSF. Friday-Saturday.*†

October 15-16—**Logical Glaucoma Therapy.** UCSF. Friday-Saturday.*†

October 16—**Imperial County Medical Society Program on Emergency Room Treatment.** Barbara Worth County Club. Saturday. 8 hours. Contact: Imperial County Medical Society, El Centro.

October 20-April 20—**Basic Science Course in Ophthalmology.** UCLA. Wednesdays. Lecture: 49 hours, Lab: 31½ hours. $175 for full course.

October 22-24—**California Society of Internal Medicine Annual Meeting.** Hotel Del Coronado, Coronado. Friday-Sunday. Contact: Nancy V. Louw, executive secretary, California Society of Internal Medicine, 350 Post Street, San Francisco 94108.

October 23—**Endocrine and Metabolic Disorders.** UCSF at Childrens Hospital, San Francisco. Saturday.*†

October 23—**Obstetrics and Gynecology Annual Fall Seminar.** Auditorium of the Santa Clara County Administration Building, 70 West Hedding Street, San Jose. Saturday from 8:30 a.m. to 4:30 p.m. Contact: Howard W. Christopher, M.D., secretary, Shufelt Society of Santa Clara County, 621 E. Campbell Ave., Campbell.

October 23-24—**Practical Management of Surgical Problems.** UCSF at Franklin Hospital, San Francisco. Saturday-Sunday.*†

October 24-27—**California Academy of General Practice Annual Scientific Assembly.** Statler Hotel, Los Angeles. Sunday-Wednesday. 13 hours. Contact: Mr. William W. Rogers, executive secretary, California Academy of General Practice, 9 First Street, Room 900, San Francisco.

October 27-29—**American Thoracic Society Postgraduate Course on the Evaluation of Pulmonary Function.** Stanford University School of Medicine, Palo Alto. Wednesday-Friday. 80 hours. Contact: Rudy Glover, Tuberculosis and Health Association of California, 424 Pendleton Way, Oakland.

October 28-31—**Pacific Coast Fertility Society Annual Meeting.** Sahara Hotel, Las Vegas. Thursday-Sunday. Contact: Gregory Smith, M.D., 909 Hyde Street, San Francisco 94109.

October 29—**Kern County General Hospital Postgraduate Conference.** Kern County General Hospital, 1830 Flower Street, Bakersfield. Friday. 8 hours. Contact: George A. Paulsen, M.D., chairman, Postgraduate Conference Committee, Kern County General Hospital.

October 29-30—**Arthritis in Practice.** UCSF. Friday-Saturday.*†

October 29-31—**Southern California Psychiatric Society Annual Convention.** Santa Barbara Biltmore Hotel. Friday-Sunday. Contact: Ralph M. Obler, M.D., 11860 Wilshire Blvd., Los Angeles 90025.

NOVEMBER

November 5-6—**California Hospital Seminar on the Acute Abdomen.** California Hospital, 1414 South Hope Street, Los Angeles. Friday-Saturday. 12 hours. Contact: Kenneth L. Senter, M.D., Director of Medical Education, California Hospital.

November 5-6—**Diseases of the Biliary System.** UCSF. Friday-Saturday.*†

November 6-7—**Postgraduate Seminars in Psychiatry.** UCSF at Fresno Community Hospital, Fresno. Saturday-Sunday.*†

November 10—**The Southern California Annual Science Lecture of The American College of Physicians.** Statler Hilton Hotel, Los Angeles. Wednesday, 6:30 p.m. Contact: W. Philip Corr, M.D., Governor for Southern California, The American College of Physicians, 3660 Arlington Avenue, Riverside 92506.

November 11-13—**Gerontological Society.** Ambassador Hotel, Los Angeles. Thursday-Saturday. Contact: Mrs. Marjorie Adler, MA, Gerontological Society, 661 S. Euclid, St. Louis 63110.

November 11-13—**Annual Western Institute on Epilepsy.** Kona Kai Club, Shelter Island, San Diego. Thursday-Saturday. $10. Contact: Manuel Barba, M.D., San Diego County Epilepsy Society, 1612 30th Street, San Diego 92102.

November 12-13—**Kaiser Foundation Hospitals Symposium on Genetics.** Statler Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Herman Weiner, M.D., Permanente Medical Group, 1505 North Edgemont, Los Angeles 90027.

November 13-14—**First Annual Clinical Cancer Conference.** UCSF. Friday-Saturday.*†

November 14—**Current Cancer Chemotherapy.** UCLA at Glendale Sanitarium—Annual Meeting. Sunday.*†

November 16-17—**Albert M. Snell Memorial Lectures.** Presented by the Palo Alto Medical Research Foundation. Palo Alto Medical Clinic Auditorium. Tuesday and Wednesday evenings at 8:00 p.m. Contact: Edward E. Daleske, assistant director, Palo Alto Medical Research Foundation, 860 Bryant St., Palo Alto.

November 17—**Santa Barbara Cottage and General Hospitals Program on Advances in Medical Practice.** Santa Barbara Cottage Hospital. Wednesday. 3 hours. Contact: C. A. Domz, M.D., 317 West Pueblo, Santa Barbara.

November 19-20—**Musculoskeletal System: Congenital and Heritable Defects.** UCSF. Friday-Saturday.*†

DECEMBER

December 1-4—**Ophthalmology Symposium: Retinopathy and Diabetes.** UCSF. Wednesday-Saturday.*†

December 3-4—**Vectorcardiography.** UCSF. Friday-Saturday.*†

December 11—**Medical Emergencies.** Pres. Med. Ctr. Saturday.*†

December 11-12—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton. Saturday-Sunday.*†

JANUARY

January 19—**Riverside County General Hospital Postgraduate Assembly.** Riverside County General Hospital. Wednesday. 12 hours. Contact: Harold A. Roth, M.D., Riverside County General Hospital, 9851 Magnolia Avenue, Riverside 92503.

January 20-21—**New and Old Antibiotics.** USC. Thursday-Friday.*†

January 22—**Pediatric Cardiology Symposium.** Pres. Med. Ctr. Saturday. 8 hours.†

January 28—**Nuclear Medicine.** USC. Friday.*†

January 28-30—**Clinical Conference in Pediatric Anesthesiology.** Friday-Sunday. Contact: M. Digby Leigh, M.D., Childrens Hospital of Los Angeles, 4614 Sunset Blvd., Los Angeles 90027.

January 29—**Practical Proctology.** Pres. Med. Ctr. Saturday. 8 hours.†

January 31-February 1—**Uroradiology.** UCLA. Monday-Tuesday.*†

FEBRUARY

February 1-April 19—**Bedside Cardiology.** USC at Los Angeles County Hospital. Tuesdays.*†

February 9—**Symposium on Shock.** USC. Wednesday.*†

February 10-11—**Symposium on Endocrinology.** USC. Thursday-Friday.*†

February 11-13—**American College of Physicians, Northern California and Nevada Regional Meeting.** Mark Thomas Inn, Monterey. Friday-Sunday. 10 hours. Contact: Roberto F. Escamilla, M.D., Governor, Northern California and Nevada Region, American College of Physicians, 897 Hyde Street, San Francisco.

February 12—**Surgical Emergencies.** Pres. Med. Ctr. Saturday. 8 hours.†

February 14-16—**Institute for Metabolic Research Dynamics of Endocrine and Metabolic Disease Annual Symposium.** Highland Hospital. $30. Contact: L. W. Kinsell, M.D., director, Institute of Metabolic Research, 2701 14th Ave., Oakland.

February 16-20—**Controversial Areas in Surgery.** UCLA at Palm Springs. Wednesday-Sunday.*†

February 20-23—**Current Concepts in Chemotherapy.** UCLA at Palm Springs. Sunday-Wednesday.*†

February 24-25—**Medical-Surgical Gastroenterology Conference.** USC. Thursday-Friday.*†

February 25-26—**Workshop on Hand Injuries.** Pres. Med. Ctr. Friday-Saturday. 12 hours. $75.

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The Physician's BOOKSHELF

HUMAN TUMOURS SECRETING CATECHOLAMINES—Clinical and Physiological Study of the Pheochromocytomas—Henri Hermann, Correspondent de l'Institutand Professor of Physiology, and René Mornex, Associate Professor of Medicine, Faculté de Médicine, Lyon. Translated by Dr. R. Crawford. A Pergamon Press Book distributed by The Macmillan Company, New York, 1964. 207 pages (No price quoted).

The authors of this book present the reader with the benefit of long experience in the clinical and laboratory aspects of pheochromocytoma. In addition, they cover the pertinent literature well. This material is organized in the masterful fashion of a first-rate professor, giving (when possible) a unified viewpoint to facilitate understanding but at the same time acknowledging conflicting data. This viewpoint is summarized in a few lines at the beginning of each chapter, and this summary gives the reader sufficient acquaintance with the chapter to decide whether to read it for more detail.

The book is based on 507 cases of pheochromocytoma, including the authors' own series and other cases published in enough detail to be summarized according to a standard plan. At the time of writing, these 507 cases were about half of the total pheochromocytomas in the world literature. The cases are referred to repeatedly, especially in the chapters on the clinical features of the disease. The pertinent individual cases are detailed in tabular form in the discussion of the less common manifestations of pheochromocytoma: severe associated diabetes or premature coronary arteriosclerosis, asymptomatic forms, instances of tumors whose first manifestation was fatal, intraadrenal nonexpansive tumors, intrathoracic and intravesical forms, multiple tumors operated on in two stages, malignant pheochromocytomas, familial forms (with pedigrees in each instance), cases associated with von Recklinghausen's Disease, tumors developing during childhood but diagnosed in later years, and cases revealed by pregnancy. Throughout the book, the authors illustrate their points with pertinent case histories and with tables and figures based on the 507 cases.

The book is organized into the following sections: I. Clinical Features (cardiovascular manifestations, metabolic and endocrine manifestations, unusual features, anatomical distribution, association with other conditions); II. Diagnosis (clinical exam, pharmacodynamic tests, measurement of catecholamines and their metabolites, radiologic studies) and Treatment; III. Anatomical and Biological Investigation (of the tumors); and IV. Physiopathology. The sections on Clinical Features and on Diagnosis and Treatment will be of most interest to the clinician. They are also better presented and freer of speculation than are the later sections. The chapters about research on the tumors themselves are interesting, but the number of cases is relatively small, and statistical analysis of the data is lacking. The final section on Physiopathology is weak, perhaps because the authors have drawn for it primarily from the published work of others rather than from their personal studies. Portions of this section (e.g. that on the thyroidal effects of catecholamines) consist of a series of reports of unrelated conflicting studies. Even here, the authors have presented their interpretation, but its foundation is shaky.

We must be grateful to Dr. R. Crawford for making this excellent work available to English speaking readers. However, the translation itself is not well done. The language is unnecessarily stilted and "Latinized" suggesting that the translation was direct, with little change from the original French form. Some words which appear repeatedly were unfamiliar to this American reader, although they can be found in a medical dictionary. Examples are "semiology" (symptomalology), "polyglobulism" (polycythemia), "nycturia" (nocturnal) and "meteorism (tympanites). Other terms seem awkward though understood: "interrogation" for "history" and "error from deficiency" for "false negative." Despite these problems, the work is quite readable, and it is well worth overcoming the problems of style in order to benefit from the content of this excellent monograph.

MARGUERITA T. HAYS, M.D.

* * *

REPORT OF THE COMMISSION ON DRUG SAFETY—Commission on Drug Safety; (founded by the Pharmaceutical Manufacturers Association) L. T. Coggeshall, M.D., Chairman. Orders for this Report should be addressed to: Federation of American Societies for Experimental Biology, 9650 Wisconsin Avenue, N.W., Washington, D.C. 20014. 228 pages.

As a result of the Kefauver-Harris food and drug law and subsequent regulations of the U.S. Food and Drug Administration, a Commission on Drug Safety was founded by the Pharmaceutical Manufacturers Association with a grant-in-aid in 1962. Lowell T. Coggeshall, M.D., Vice-President of the University of Chicago, was appointed chairman and was asked to appoint to the Commission individuals who were well-informed in the field of drug safety. Fourteen such persons were appointed, representing universities, the pharmaceutical manufacturing industry and the American Medical Association. The Commission held monthly meetings from September, 1962 until March, 1964, reviewing and evaluating the reports of 17 subcommittees, only 8 of which had members of the Commission as chairmen. This book is the report of the Commission.

Nearly $1 billion is now invested annually in medical research, of which a large share is spent in creating and investigating new drugs. This has led to the introduction of many effective therapeutic agents, some of which have undesirable or dangerous side effects. Items discussed include the importance of basic animal research, not only to perform standard pharmacological and toxicological tests, but also to devise tests which will predict the hazards of teratogenic effects, effects on blood cells and bone marrow, and skin rash. Basic research must be greatly expanded to provide a broad base of fundamental knowledge necessary to anticipate and interpret drug effects. The Subcommittee on Tertology recommended that thalidomide be intensely studied since it is not known why this drug is toxic to human embryos but not to embryos of other mammals.

The first trials of a drug on human subjects (Phase 1) should be carried out by a clinical pharmacologist to obtain information about dose range, absorption and excretion of the drug, demonstrable effects of the drug on the subject, undesirable side effects and safety. Phase 2 also should be carried out by a small number of specially trained investigators who test the drug against disease states or for prophylactic purposes. Phase 3 is an expansion of phase 2 with investigations by a larger number of physicians using the drug in both hospital and office practice with a large number of patients involved. "Since the patient's right to good medical care cannot be compromised, the judgment and professional skill required of an investigator, particularly in the early phases of clinical evaluation, must be of the highest order." However, the Commission does not think that clinical investigation should become a medical specialty, except for Phase 1 which requires the services of a clinical pharmacologist, who should be a member of a department of pharmacology, collaborating with members of clinical departments in either a university or a research institute.

Support for the studies and training of investigators should be the responsibility of the pharmaceutical industry, private philanthropy, the universities and the government, in a cooperative fashion.

To adequately review this important report, which will for years influence the testing of new drugs and their approval by the federal and state Food and Drug Administrations, would require several pages. The reviewer will close the discussion with a few quotations.

"Drug safety in itself is not and cannot be the first consideration of the manufacturer, nor of the physician. The governing principle must be to provide the best possible therapy for the patient, and this means that the possible risk inherent in new compounds must be weighed against potential gains in efficacy. The seriousness of the illness, quite clearly, dictates the margin of allowable risk."

"Industry should intensify its collaboration with government scientists to work towards better mutual understanding of the need, usefulness, and significance of existing and proposed toxicity tests."

There should be "a continuing Committee on Toxicity Tests which would include qualified scientists from government, industry, and other fields of activity."

"A single pattern for payment for services of the investigator does not exist, and it certainly merits consideration."

"The need for the Food and Drug Administration to become scientifically oriented is readily apparent. Its decisions, to protect the public and to be just with regard to drug manufacturers, must reflect the best current scientific opinion. This imposes upon the FDA two obligations . . . first, to improve its own scientific personnel resources, and second, to make improved use of available medical and scientific counsel on an advisory basis."

"Proposals to extend restrictive Federal or state legislation to the area of animal experimentation—however well intentioned—work against the interests of drug safety. . . . The Commission believes that any codification of standards for the handling of laboratory animals imposes on the scientist a measure of inflexibility that is both demeaning to the scientist and incompatible with his freedom to investigate."

Clinton H. Thienes, M.D.

* * *

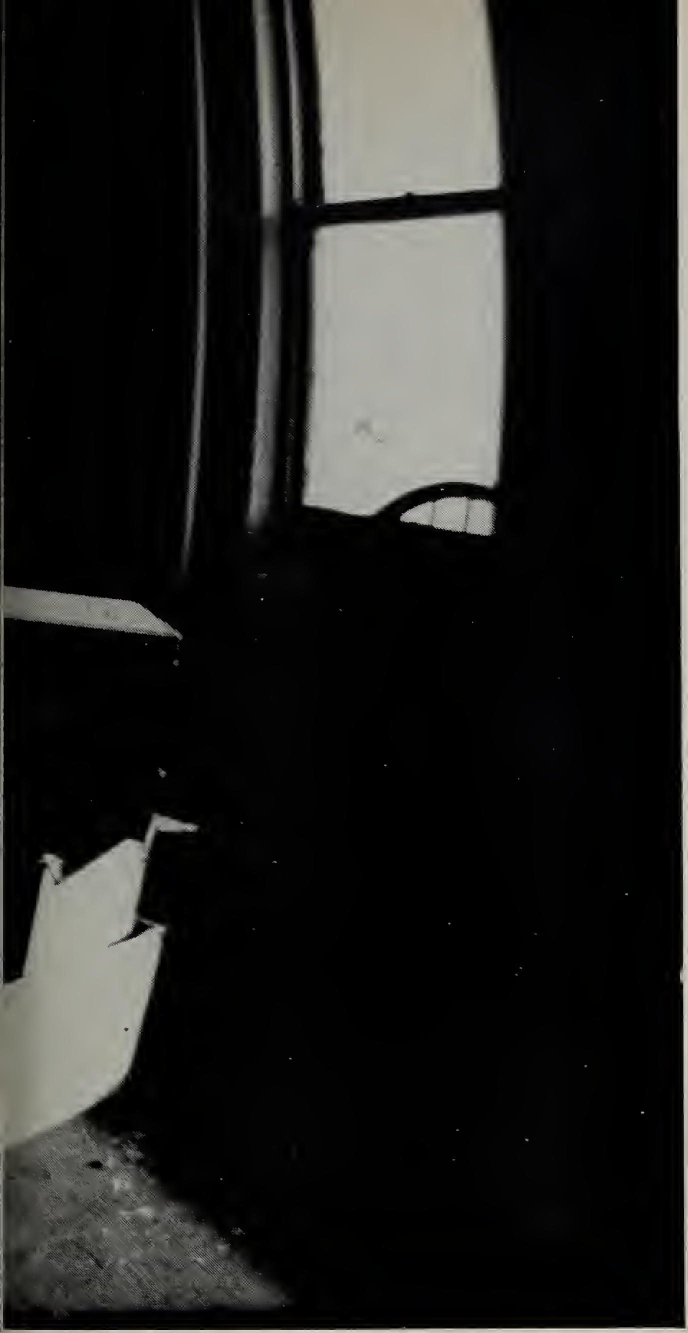
CEREBRAL INFARCTION—Alan Barham Carter, M.A., M.D.(Camb.), F.R.C.P., D.P.M.(London), Physician and Neurologist to the Ashford Hospital, Middlesex; Consulting Neurologist to the Queen Alexandra Military Hospital, London, S.W. 1; Adviser in Neurology to the War Office. Foreword by Lord Brain, F.R.S., D.M.(Oxon.), F.R.C.P. (London), Consulting Neurologist to the London Hospital and Consulting Physician to the Maida Vale Hospital for Nervous Diseases. A Pergamon Press Book distributed by The Macmillan Company, New York, 1964. 209 pages, $9.50.

Any physician who treats adults will encounter the problem of stroke. Here in one slim volume is an up-to-date discussion of the anatomy (with Frank Netter plates), pathogenesis, clinical classification, differential diagnosis and treatment of cerebro-vascular disease. Dr. Carter has given us the benefit of a careful literature review as well as his own extensive experience. His approach would be acceptable anywhere in the United States, although he is less enthusiastic about vascular surgery and arteriography than many Americans. He devotes two chapters to anti-coagulant therapy, but arrives at the same discouraging conclusion as most major studies: there are only a small number of patients who can be expected to benefit from anti-coagulants, and the risks of their use are considerable.

"With regard to atheromatous cerebral infarction, anticoagulant therapy is mainly contraindicated excepting for normotensive patients with a *progressing* (reviewer's italics) cerebral infarction, where the diagnosis is as far as humanly possible beyond all doubt. Long term anticoagulant therapy is dangerous and ineffectual in preventing further infarction or in prolonging life, although it appears to prevent transient ischemia episodes. It seems that only one patient in ten with cerebral infarction is suitable for anticoagulants."

Sections on rehabilitation and home and hospital care are excellent and contain many useful hints. On the whole, however, the book leaves the reader with more frustration than hope—an attitude that pervades the field of cerebrovascular diseases. This may stem, in part, from the discouragingly small role the physician can play in the care of the patient. Once the diagnosis is established, treatment consists almost entirely of good nursing care and good physical therapy. This puts the doctor almost completely out of the picture. In cardiac infarction there are powerful drugs like digitalis, quinidine, anticoagulants and vaso-pressors to consider, the frequent EKG's to examine and serum enzyme levels to mull over, and the physician feels that he alone can manage the case. Unless the present enthusiasm for vascular surgery spreads, or is replaced by some equally exciting tool, it will continue to be difficult to interest the medical profession in the problems of cerebral infarction. Until then, however, we all have to take care of the stroke victim as best we can. Dr. Carter's little book provides a useful summary of what we have to offer at the present time.

J. E. Holmes, M.D.



Side effects and precautions: The transitory drowsiness which may occur with hydroxyzine HCl usually disappears spontaneously in a few days with continued therapy, or is correctable by dosage reduction. Dryness of the mouth may be seen with higher doses. Involuntary motor activity has been reported in hospitalized patients on higher than recommended doses. Hydroxyzine HCl may potentiate CNS depressants, narcotics such as meperidine, barbiturates, and anticoagulants. In conjunctive use, dosage for these drugs should be decreased. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. **Parenteral Solution Precautions and contraindications:** This dosage form is intended only for I.M. or I.V. administration and should not, under any circumstances, be injected subcutaneously or intra-arterially. When the usual precautions for I.M. injection have been followed, reports of soft tissue reactions have been rare. I.V. administration should be slow, no faster than 25 mg. per minute, and should not exceed 100 mg. in any single dose. Particular care should be used to insure injection only into intact veins; a few instances of digital gangrene occurring distal to the injection site have been attributed to inadvertent intraarterial injection or periarterial extravasation, both of which should be avoided. **More detailed professional information available on request.**

Supplemental Sex Education Urged

Schools and communities are urged to take more responsibility in supplementing the home in teaching facts about sexual reproduction and the values of the family system in a recent statement of the Joint Committee on Health Problems in Education.

Recognizing that preventive measures such as better sex instruction by parents and schools "will be slow in effecting results" with respect to the problem of early and unwanted pregnancies, the Committee re-emphasized its statement of 1963 urging schools and communities to "devise a plan for the continued education for married students and unwed parents."

The Committee has been a cooperative effort for the past 54 years of the National Education Association and the American Medical Association.

In another statement, the Committee cautioned schools and colleges against using hypnosis as a form of entertainment, and recommended that students should be discouraged from practicing hypnosis.

"In accordance with the statement of the Council on Mental Health of the American Medical Association, the Joint Committee on Health Problems in Education recognizes that hypnosis has been placed in the framework of psychiatry and psychodynamic psychology. The Council on Mental Health warns that except under the most carefully controlled medical conditions, hypnosis can be dangerous," the Committee said.

FAMILY RULES—D. D. Jackson (Mental Research Institute, Palo Alto, Calif.). Arch. Gen. Psychiat., 12:589 (June) 1965.

The author contends that because marriages are invariably composed of one man and one woman, the sexual aspect of marriage has been over emphasized. This applies both to sexual relations and to so-called male and female roles. The author points out that there is no known human relationship equivalent to the long-term, enduring, collaborative aspects of marriage, and therefore it may be a mistake to blame marital failure on the woman being unfeminine or the man not being "masculine enough." Instead, the author believes there are typical rules for marriage which involve a quid pro quo basis and examples of such rules are discussed.

* * *

MYELOMA PROTEINS AND THE CLINICAL RESPONSE TO MELPHALAN THERAPY—D. E. Bergsagel, P. J. Migliore and K. M. Griffith (M. D. Anderson Hosp. and Tumor Institute, 6723 Bertner Ave., Houston). Science, 148: 376-377 (April 16) 1965.

The responses of 132 myeloma patients treated with melphalan were studied. All of the patients producing only Bence Jones kappa proteins showed objective improvement after therapy. Half of the patients with myeloma serum proteins showed improvement. Melphalan therapy was not successful in any of the patients who produced only Bence Jones lambda proteins.

Mutilation or Prophylactic Surgery?

In his many years of medical practice in northern Morocco, Charles A. Apffel, M.D., met many patients who had no uvula, the fleshy pendant at the back of the soft palate.

He discovered that the ancient custom of surgical removal of the uvula in early childhood persists among certain Moroccan tribes.

Dr. Apffel made another discovery: in none of more than 200 persons on whom the operation had been performed could he see or feel any trace of tonsils or adenoids. The child's regional lymphoid tissue simply doesn't develop after the operation, he concluded.

"Such individuals may contract a diffuse pharyngitis, but never a tonsilitis or adenoiditis," Dr. Apffel wrote in the July 12 *Journal of the American Medical Association.*

Uvulectomy's bearing on reduction of rheumatic fever or chronic arthritis can only be suspected, Dr. Apffel said. However, eliminating the uvula gets rid of one center of infection, he pointed out.

Uvulectomy, as practiced in northern Morocco, has no religious motivation and is not related to any of the rites enjoined in the Koran, Dr. Apffel said. It is transmitted from generation to generation as a family tradition. It is meant to aid breast feeding and speech.

The operation is customarily performed by the sexton of the neighborhood mosque, or by a barber. Many Moroccan barbers still act as practical surgeons.

"Whatever the consequences of neonatal uvulectomy, they point to a close interdependence between the uvula and the constituents of the Waldeyer ring (the adenoidal tissue formed by the lingual, pharyngeal, and faucial tonsils)," Dr. Apffel said.

He suggested that the custom may have originated in the ancient Spanish medical schools, and then been transferred to northern Morocco when the Moors were forced out of Spain.

Dr. Apffel is on the staff of Pondville Hospital, Walpole, Mass.

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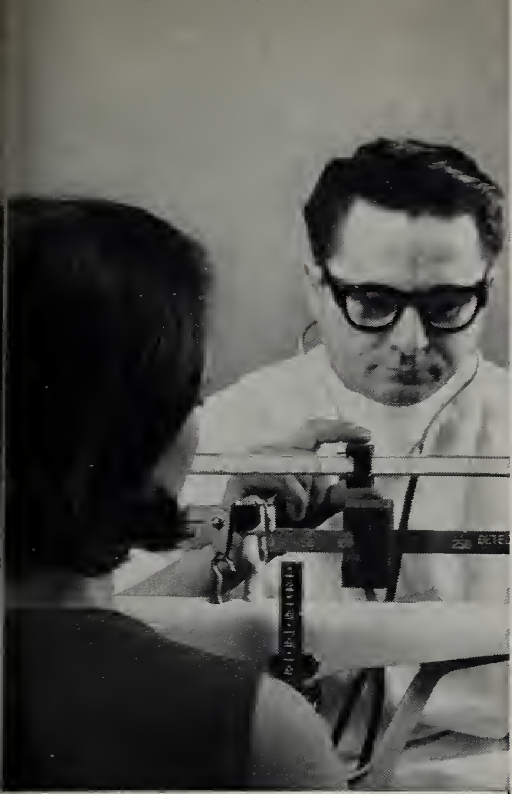

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AMA Recommends an Exercise Test

A simple test which may detect some children's health problems during their school physical education class is being recommended by the American Medical Association.

The "four-minute step test" is intended to determine a child's response to moderately strenuous exercise. The test is not an overall estimate of physical fitness, but if a child does poorly on it, he may need medical attention.

Physical education instructors are being told about the test and its uses in a report by the AMA's Committee on Exercise and Physical Fitness.

The test consists of stepping up and down a platform 14 to 20 inches high, 30 times a minute for four minutes. Pulse rates are taken one, two and three minutes after the exercise. Pulse recovery is rated on a scoring system.

If your child takes the test in school this fall, the instructor will be looking for possible health danger signals, as well as checking the child's response to exertion.

Some of these danger signs are excessive breathlessness, pale or clammy skin, persistent shakiness or muscle twitching after exercise, bluing of lips, or unusual fatigue.

Other symptoms may also be cause for medical referral. These include headache, dizziness, fainting, digestive upset, pain not associated with injury, undue pounding or uneven heartbeat, and disorientation or personality changes.

"The instructor should remember that some of the symptoms and signs enumerated above are transient and may indicate only that a boy or girl is physically unfit," the committee said. "With careful, progressive conditioning in such cases, not only will the reactions finally disappear, but the boy or girl will eventually begin to enjoy physical activity. Only a physician, however, should attempt to distinguish between a lack of fitness and some incipient health problem."

To determine the "recovery index," the three pulse counts taken after the test are added.

When the three 30-second pulse counts total:	*The response to the test is:*
199 or more	Poor
171 to 198	Fair
150 to 170	Good
133 to 149	Very Good
132 or less	Excellent

When a youth fails to complete the test or does poorly, medical referral may be desirable.

Young people whose previous health history indicates the possibility of rheumatic or other form of heart disease should not take the test or similar strenuous exercise without medical clearance. The same rule applies to students with other serious

(Continued on Page 17)

Side effects and precautions: The transitory drowsiness which may occur with hydroxyzine HCl usually disappears spontaneously in a few days with continued therapy, or is correctable by dosage reduction. Dryness of the mouth may be seen with higher doses. Involuntary motor activity has been reported in hospitalized patients on higher than recommended doses. Hydroxyzine HCl may potentiate CNS depressants, narcotics such as meperidine, barbiturates, and anticoagulants. In conjunctive use, dosage for these drugs should be decreased. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. **Parenteral Solution Precautions and contraindications:** This dosage form is intended only for I.M. or I.V. administration and should not, under any circumstances, be injected subcutaneously or intra-arterially. When the usual precautions for I.M. injection have been followed, reports of soft tissue reactions have been rare. I.V. administration should be slow, no faster than 25 mg. per minute, and should not exceed 100 mg. in any single dose. Particular care should be used to insure injection only into intact veins; a few instances of digital gangrene occurring distal to the injection site have been attributed to inadvertent intraarterial injection or periarterial extravasation, both of which should be avoided. **More detailed professional information available on request.**

Leukemia Patterns Are Changing

Leukemia remains an invariably fatal disease, but improved medical treatment is attacking some of the causes of its victims' deaths. As a result, some of these persons are living longer.

A report in the July 12 *Journal of the American Medical Association* noted "striking changes" during the past 10 years in the natural history of acute leukemia among patients at the National Cancer Institute, Bethesda, Md. The report also notes the increasing survival time of patients under age 20 who have acute lymphatic leukemia.

"In general, there has been a marked decline in the number of patients dying of hemorrhage and a sharp increase in the incidence of fatal infection," the report said.

This takes note of the fact that some anti-tumor treatment breaks down the body's infection defenses. Thus, some kinds of infection rise as hemorrhages decline. Even though they eventually died, however, many leukemia victims' lives were prolonged because doctors were able to stave off one or another of the causes of death.

The report credited improvements in treatment, such as specific antileukemic agents, combination chemotherapy programs, and blood platelet and granulocyte transfusions, for the change in leukemia patterns over the 10-year period.

Four physicians from the Acute Leukemia Service of the National Cancer Institute surveyed the records of 444 leukemia victims who died there between 1954 and April 30, 1963. The authors are Evan M. Hersh, M.D., Gerald P. Bodey, M.D., Boyd A. Nies, M.D., and Emil J. Freidreich, M.D.

The study was undertaken to assess the effect of the new therapeutic measures on the course of acute leukemia.

"A striking finding of this study is the decline in fatal hemorrhage subsequent to platelet transfusion therapy," the report said.

All hemorrhage declined from 66.8 per cent at the start of the 10-year period to 37.2 per cent at the end.

Since patients regularly received platelet transfusions after 1960-61, "it is probable that the decline in hemorrhage is related to this added therapeutic measure," the report said.

The authors noted, however, that it is difficult to secure enough platelets for large adults. Platelet transfusions have less success during periods of hemorrhage and infection.

Chemotherapy and such supportive measures as platelet transfusion are responsible for the improved survival of patients under age 20, the authors said. An earlier study found that patients receiving antibiotic and transfusion therapy survived an average of 8.9 months, compared to 5.6 months for untreated patients.

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Cautious View of Lung Ailments

Physicians know that a variety of substances, when inhaled, can cause serious lung disease.

However, three reports in the July 26 *Journal of the American Medical Association* illustrate why doctors continue to be cautious in citing a specific cause for some lung ailments.

One report by three Wisconsin physicians indicates that those who keep pigeons as a hobby may be susceptible to a newly observed disease called Pigeon Breeder's Lung. Three patients suffered breathing difficulty and chills, fever, and cough after handling pigeons. Several other pigeon handlers tested, however, reported no ill effects from being near the birds. The disease appears to be another of several recently studied pulmonary disorders in which the patient develops an extreme sensitivity to the material or animals he is handling, the report said.

A second JAMA report cited two cases of pulmonary granulomatosis, or multiple small lung tumors, in connection with the inhalation of hair spray and aerosol deodorant. Whether hair sprays and related cosmetic aerosols cause disease in man has been hotly contested, the report noted. The authors—five physicians at Jewish Hospital, Brooklyn, N.Y.—do not state that aerosols caused the tumors in their patients. They offer three possibilities: (1) that the disease of their patients was sarcoidosis, a lung ailment of unknown cause, and that exposure to aerosols was only incidental, (2) that the patients' lung lesions were responses to an agent present in the aerosols, or (3) sarcoidosis can be provoked by an agent in aerosols.

On the other hand, Chicago and Los Angeles researchers in a third report state that they were unable to produce lung lesions in dogs exposed for up to two years to large amounts of hair spray. Earlier medical reports also have noted the difficulty of producing lung ailments experimentally with hair spray and the low incidence of lung disease despite the massive use of these sprays.

Finally, a JAMA editorial in this same issue said: "To attempt a summary or to present conclusions concerning thesaurosis (lung disease following exposure to aerosol hair sprays), pigeon flyers' disease, or even the older granulomatous diseases would be premature at this time.

"We may expect that in the next few years this whole area of pulmonary granulomatous disease and 'allergic lung disease' will be seen with increasing frequency. . . . Clearly, the problem of pulmonary granuloma is far from being solved."

The report on Pigeon Breeder's Lung is by Charles E. Reed, M.D., Abe Sosman, M.D., and Robert A. Barbee, M.D., of the department of medicine, University of Wisconsin, Madison, and Wood Veterans Administration Hospital, Milwaukee.

The report on two cases of lung disease was by Michael A. Nevins, M.D., George H. Stechel, M.D., Stanley I. Fishman, M.D., George Schwartz, M.D., and Arthur C. Allen, M.D., of Jewish Hospital, Brooklyn, N.Y.

The report on experimental exposure of dogs to hair spray was by Robert P. Giovacchini, Ph.D., medical department, the Toni Company; Gerald H. Becker, M.D., Michael Reese Hospital and Chicago Medical School; Matthew J. Brunner, M.D., California College of Medicine, Los Angeles, and Frank E. Dunlap, M.D., Northwestern University School of Medicine, Chicago.

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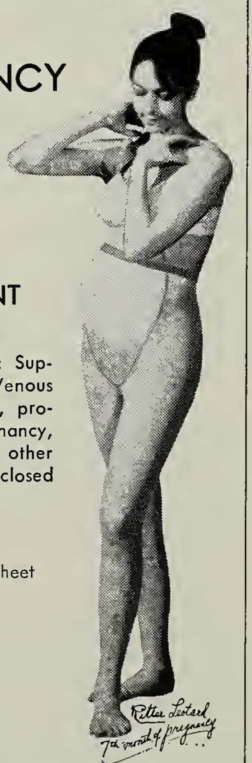

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PULMONARY EMBOLISM

ARTHUR SELZER, M.D., *San Francisco*

■ *Pulmonary embolism occurs in three forms: (1) Asymptomatic "silent" embolization of lungs; (2) pulmonary infarction; and (3) massive pulmonary embolization leading to acute cor pulmonale. The commonest source of emboli are veins of the lower extremities and of the pelvic organs. The prevention and the treatment of pulmonary embolism overlap, for except for the heroic procedure of pulmonary embolectomy, treatment is equivalent to the prevention of further emboli. The diagnosis may be easy in typical cases and very difficult in others.*

PULMONARY EMBOLISM occurs in three principal forms: (1) As asymptomatic occlusion of a branch of the pulmonary artery, "silent" pulmonary embolus; (2) as an occlusion of such a vessel producing an anatomic change in the lung supplied by the occluded branch—pulmonary infarction; and (3) as a sudden large-scale occlusion of the inflow to the lungs—either single massive embolism or multiple large emboli—which produces sudden overloading of the pulmonary circulation leading to right heart failure and is often fatal. It is this third, serious form of pulmonary embolism with its dramatic suddenness that has made this condition one of the most dreaded diseases of the circulatory system.

The source of embolization of the pulmonary arterial tree is the entire venous system. However, experience has shown that certain portions of it —deep veins of the legs and the veins draining the pelvic organs—are particularly prone to intravascular thrombosis. The most important predisposing factors for intravenous thrombosis are: (a) stasis; (b) trauma; and (c) states of hypercoagulability of the blood. Venous thrombosis may occur in its pure form, without affecting the vein itself, *phlebothrombosis,* and as an inflammatory disease of the vein associated with thrombosis, *thrombophlebitis.* The former may be clinically apparent by the resulting fluid retention in the affected extremity, or it may be "silent." The latter represents an easily recognizable clinical syndrome. The probability of pulmonary embolization is very much higher in phlebothrombosis than in thrombophlebitis.

The prevention of pulmonary embolism is tantamount to prevention of intravascular clotting within the venous system. The problem obviously cannot be entirely eliminated but a significant reduction of it is attainable by avoiding or minimizing the predisposing factors. The prevention of pulmonary embolism is made more difficult by the fact that intravenous thrombosis might occur not only in ill persons but in healthy ones as well. It is well known that during World War II the incidence of pulmonary embolism increased significantly among the the population that slept in cramped positions in air-raid shelters; long airplane rides are known to have precipitated phlebothrombosis and pulmonary embolization in otherwise healthy persons. However, the prime

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From the Cardiopulmonary Unit, Presbyterian Medical Center, San Francisco.

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target for preventive approach to the problem of pulmonary embolism is the patient with a known tendency to venous stasis—the patient with low cardiac output, the patient confined to bed rest for any length of time and the patient with an immobilized extremity. It was the fear of pulmonary embolization that led the surgeons to institute early postoperative ambulation some two decades ago and that has brought about the widespread use of passive leg exercises and of elastic bandages for patients confined to bed, particularly in elderly persons and patients with heart disease.

Diagnosis

In some cases the diagnosis of pulmonary embolism may be so easy as to be virtually self-evident; in others it may be impossible to make. Everyday experience at the autopsy table has shown that in patients who die in cardiac failure, pulmonary infarct due to embolization is extremely common, but not often suspected clinically. The diagnostic approach to the problem has to be considered separately for the three principal forms of it.

Silent pulmonary embolism. As the name implies, many pulmonary emboli have no clinical clue as to their occurrence—even in retrospect when their presence is later demonstrated by further development or at autopsy. The most important clinical form of silent pulmonary embolism consists of gradual and progressive occlusion of the pulmonary arterial tree. In contrast to the acute form, chronic low-grade pulmonary embolization leads to pulmonary hypertension and right ventricular failure unassociated with any recognizable episodes. This clinical syndrome is in reality one of the "obscure" forms of pulmonary hypertension, indistinguishable from primary pulmonary hypertension. The correct diagnosis of the embolic nature of pulmonary hypertension (after having ruled out congenital and acquired heart disease with secondary involvement of the pulmonary vasculature) can only be made on the basis of probability. It has been demonstrated that women in the childbearing age are particularly prone to silent pulmonary embolization with pulmonary hypertension. There appears to be a definite relationship to pregnancy in that signs of pulmonary hypertension and cardiac difficulty are apt to occur weeks or months after pregnancy. The pulmonary vascular obstruction here may be related to thrombotic or to amniotic emboli with deposition of organized fibrin in small branches of the pulmonary vascular tree.

In addition to repetitive silent pulmonary embolization masquerading as primary pulmonary hypertension, pulmonary embolism leading to clinically inapparent lung infarcts is, as mentioned, a common occurrence in patients with cardiac failure. In such patients aggravation of cardiac failure and lack of response to treatment may be manifestations of pulmonary embolism.

Pulmonary infarct. Typical pulmonary infarct manifests itself clinically by sudden onset of thoracic pain of the pleural type, by some dyspnea, usually not too pronounced, and by hemoptysis. If these events occur in a person who has either clinical evidence of phlebothrombosis or thrombophlebitis, or is a candidate for it by virtue of rest or immobilization of a part of the body—then the diagnosis is certain. In such cases, radiographic examination of the chest usually provides confirmation by showing a circumscribed pulmonary shadow (rarely "wedge shaped") or "disc atelectasis." The course of pulmonary infarct is usually benign. The patient may have elevation of temperature, usually of short duration; hemoptysis is apt to stop within two or three days, and radiolucency of the lungs is restored within less than a week, sometimes even within a day or two.

Often the symptoms of pulmonary infarct are atypical, making for diagnostic difficulties. The principal clue to the diagnosis is the presence of a condition conducive to phlebothrombosis. Thus, in patients who are on bed rest or have an immobilized part of the body, any sudden development of pulmonary disease is suspect. On the other hand, obscure hemoptysis or pleural pain appearing without a respiratory infection justifies a careful search for thrombophlebitis, for Homans' sign, for unilateral ankle edema or for inequality in circumference of the two calfs. Because of the ephemeral nature of changes in roentgenograms of the chest, it often pays off to order chest films every day or two if pulmonary infarct is suspected.

In patients with chronic cardial disease, as has been mentioned, pulmonary infarcts occur more frequently than is clinically suspected. Silent infarcts have already been discussed. Atypical pulmonary infarcts may be manifested by sudden change in the patient's condition. Unexplained rises in body temperature, attacks of dyspnea or exacerbations of cardiac failure should arouse suspicion of pulmonary infarct. Differentiating between pulmonary infarction and pulmonary infection in patients with chronic cardiac disease is almost impossible unless specific clues pointing to one or the other happen to be present. The diagnosis of pulmonary infarction rests entirely with the clinician and is based on his clinical evaluation. The non-specificity of the radiographic changes has already been discussed. No specific laboratory test exists which would be of assistance.

Massive pulmonary embolism. While between pulmonary infarction and massive pulmonary embolism there is only a difference in degree, the clinical pattern of each is distinctive enough and there is relatively little overlap between the two. This stems from the fact that if there is enough obstruction of the pulmonary arterial tree to produce pulmonary hypertension, localizing signs of pulmonary infarction are as a rule absent. What is more, there usually is no infarction of the lung. It is important to appreciate that pulmonary hypertension—the essence of the clinical syndrome of massive pulmonary embolism—develops only with obstruction of a sizable portion of arterial lumen. It is known from animal experiments that constriction of the main pulmonary artery does not elevate pressure proximally to it until the lumen is reduced to less than one-third of the original lumen. It is well-known that in humans, ligation of one of the two branches of the pulmonary artery during pneumonectomy does not elevate pulmonary arterial pressure; studies with the aid of inflatable balloons have shown that occlusion of one pulmonary artery and considerable narrowing of the other is required to produce hypertension of the proximal portion of the pulmonary artery. The controversy in the literature as to whether mechanical blockage of the pulmonary arterial lumen has to develop to the extent of more than two-thirds of the cross-section, or whether sudden occlusion of a smaller segment may produce reflex pulmonary arteriolar constriction of the entire lung to bring about the same effect, is unresolved. Until incontrovertible evidence proves the existence of such a reflex, one can best assume that obstruction of the pulmonary arterial tree by thromboembolic material reaches a clinically significant point when two-thirds of it is occluded. There is only a narrow zone of such occlusion in which survival is possible; further obstruction soon reaches an intolerable level of overload, leading to fatal right ventricular failure.

Clinical features of massive pulmonary embolization, often referred to as "acute cor pulmonale" are as follows:

Chest pain occurs with moderate frequency. The pain is not of pleural character but resembles ischemic cardiac pain and may be confused with acute myocardial infarction. The pain is thought to originate in the dilated and tense pulmonary artery, or in the coronary circulation due to anoxia and a possible pulmono-coronary reflex.

Dyspnea is also a common symptom. In contrast to dyspnea as a manifestation of cardiac failure on the one hand, and of bronchial disease on the other hand, dyspnea in acute cor pulmonale seldom is associated with ausculatory abnormalities over the thorax. Sometimes such dyspnea resembles hyperventilation. Sudden onset and persistence of dyspnea unassociated with signs of left ventricular failure or bronchial asthma may be a tipoff—occasionally the only tipoff—of the true nature of the disease.

Shock is common in more severe forms of acute cor pulmonale. Its origin is still not completely understood: it may be a combination of cardiogenic shock representing a manifestation of falling right ventricular output and of reflex vasomotor collapse.

Physical examination of the cardiovascular system often shows signs of pulmonary hypertension and right ventricular failure. Visibility of jugular pulse with the patient in the sitting position is an indication of elevated central venous pressure and right ventricular failure. Increased force of right ventricular contraction may produce palpable and forceful pulsation of the left anterior portion of the thorax ("parasternal lift"); accentuated pulmonary valve closure may produce accentuation of the late component of the second sound, or a single loud sound at the upper left sternal edge. A dilated and tense pulmonary artery may cause a rubbing sound resembling pericardial friction rub.

The electrocardiogram may show two types of changes: In one type, S-waves may appear in lead I with Q-waves in lead III; R-waves in right precordial leads may increase in size and become associated with inverted T-waves in leads V1, V2 and V3; and in the other type, the pattern is that of suddenly developing right bundle branch block. Tall P-waves may appear in combination with either pattern. Non-specific S-T-T abnormalities may appear from day to day and change in serial tracing. The differential diagnosis between acute cor pulmonale and acute myocardial infarction may be difficult or even impossible. Films of the chest are rarely helpful, but occasionally may suggest reduced flow to portions of the lung by a variation of the vascular pattern.

The diagnosis of acute cor pulmonale is no longer an academic exercise. The availability and feasibility of emergency pulmonary embolectomy make it imperative that a precise diagnosis be made—not only of the presence of massive thromboembolism, but also of the location and distribution. This can be done by means of angiocardiographic techniques. Depending on whether time and facilities are available, selective angiography with dye injection into the right ventricular outflow tract or large-bolus intravenous angiocardiography can be done to determine whether a large occluding embolus is present, or the lesions are inaccessible multiple occlusions of smaller branches.

Treatment

Treatment of pulmonary embolism varies widely: On the one end of the spectrum there are cases in which nothing is done; on the other end, heroic, life-saving emergency operations involving cardio-pulmonary by-pass are performed. At present no practical methods of dissolving thrombi within the pulmonary arterial tree are available. The objective of treatment thus is: (1) To remove surgically a life-threatening pulmonary arterial embolus, and (2) to prevent formation or propagation of thrombi.

When dealing with pulmonary hypertension produced by repetitive silent pulmonary emboli, very little can be accomplished, for the diagnosis can only be made when extensive occlusive disease of the pulmonary arterial tree is already present. Whether persistence of pulmonary hypertension depends upon continuous feeding of miliary emboli has not definitely been established. There are isolated reports of cases in which pulmonary hypertension regressed after a period of anticoagulant therapy, which suggests the possibility of regressive changes in the pulmonary vasculature produced by elimination of further emboli. However, thus far not enough such cases have been documented and in most cases severe pulmonary hypertension is irreversible. It is possible that pulmonary hypertension—the end result of pulmonary embolism—may be brought about by several different mechanisms, some of them producing irreversible changes outright while in others pulmonary hypertension is retained only by continuous further embolization. Until this problem is definitely settled, it seems justifiable to use continuous, permanent anticoagulant therapy in all cases of "primary" pulmonary hypertension in which there is suggestive clinical evidence that thromboembolism may be the initiating factor.

Pulmonary infarction requires little active treatment. Being a self-limited, self-healing process, bed rest for a few days and careful observation usually suffice. The important problem, however, is the prevention of further emboli which might produce more infarct or might be of sufficient size to bring about acute cor pulmonale. Because of this, anticoagulant therapy with heparin for shorter-term treatment and coumarin derivatives for more chronic cases is considered indicated in patients with pulmonary infarction. If pulmonary infarcts appear in spite of anticoagulant treatment, surgical treatment should be considered, such as ligation of the femoral veins (in cases with demonstrable phlebothrombosis in the legs) or ligation of the inferior vena cava (complete or partial with insertion of clot-trapping devices).

Acute cor pulmonale represents a serious medical emergency, and treatment may be lifesaving. The purpose of the treatment is two-fold: (1) To support the overloaded circulation and (2) to prevent further emboli reaching the lungs. The extreme measure of pulmonary embolectomy has already been mentioned. If proper facilities exist for the performance of such an operation, emergency diagnostic studies should be performed before the operation, for the risk of such studies is usually less than the risk of operating without high probability that a removable single embolus is present.

Supporting treatment is directed against shock and cardiac failure. Digitalis is seldom effective, but the use of other, rapidly acting inotropic agents such as isoproterenol and levarterenol may be rewarding. These drugs are also pressor agents and may help control the shock as well. The prevention of further emboli has to be immediate and one can question the effectiveness of anticoagulation in such cases. Surgical interruption of the pathway of embolization, previously mentioned, has to be considered and may be extraordinarily, often dramatically, effective.

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Osteogenic Sarcoma in Children

ROBERT J. MC KENNA, M.D., AND CHARLES P. SCHWINN, M.D., *Los Angeles*

NORMAN L. HIGINBOTHAM, M.D., *New York*

■ *One hundred and thirty children less than 16 years of age with pathologically verified osteogenic (skeletogenic) sarcoma were seen during a 30-year period (1925-1955) with a minimum follow-up of ten years. This age group represents 23.6 per cent of the authors' total experience with skeletogenic sarcoma. The absolute survival for the entire series was 18.5 per cent at five years and 16.2 per cent at ten years.*

No child with an osseous tumor elsewhere than in an extremity had long-term survival. Amputation was the only "curative" method of therapy; 23 per cent of patients so treated were alive at five years and 20 per cent were alive at ten years. Radiation was never "curative" when used as the sole method of therapy, and treatment failure was higher in the group of patients who were treated with preoperative irradiation and then amputation than in the group treated by amputation alone.

Prognosis varied with the size of the tumor—the smaller the better. The most important factor in prognosis was the histologic subgrouping of osteogenic sarcoma. No evidence was found to support a belief that there are considerable differences between skeletogenic sarcomas in children and in adults.

OSTEOGENIC SARCOMA is the commonest primary malignant neoplasm of bone and, contrary to common belief, long survival is sometimes obtainable. Many of these tumors occur in the pediatric age where optimal treatment is too frequently modified by emotional considerations of the parents and by an air of hopelessness on the part of the physician—these deterrents at a time when radical surgical therapy offers the only hope.

For many years the opinion has been held that the prognosis for osteogenic sarcoma is worse in children than in adults.[1] Recently, Hayles and coworkers[4] offered evidence that age did not affect prognosis.

We[5] recently recorded our findings in a 30-year experience with osteogenic sarcoma in patients of all ages. We suggested that the term *osteogenic sarcoma* be used in the generic sense or discarded. The word *osteogenic* in this usage implies a derivation from primitive mesenchymal tissue which is normally destined to form skeletal connective tissue components. The classification includes the

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following categories: primary osteosarcoma, primary chondrosarcoma, primary fibrosarcoma, parosteal osteogenic sarcoma and secondary tumors arising in bone altered by preexisting disease or previous treatment. Schajowicz[6] suggested that the term *skeletogenic* be substituted for *osteogenic* since the latter term is sometimes used ambiguously as an interchangeable designation for osteosarcoma. Dahlin,[2] for instance, uses *osteogenic sarcoma* for osteoblastic bone sarcoma, where we use *osteosarcoma.*

Material

This report of 130 patients with osteogenic sarcoma, all under 16 years of age, represents 23.6 per cent of the total experience[5] with this neoplasm at the Memorial Center in the period 1925-55.

Pathology

The diagnosis was established in all cases after review of the clinical setting, the roentgenograms and the gross and microscopic material. The 130 tumors were subgrouped as follows: Osteosarcoma, 99 cases; chondrosarcoma, 16; fibrosarcoma, 8; parosteal osteogenic sarcoma, 4; osteogenic sarcoma arising in irradiated bone, 2; and secondary chondrosarcoma, 1. (See Table 1.)

Age and Sex

The age range was from 4 to 15 years (Chart 1). The youngest patient in each histologic subgroup was as follows: Osteosarcoma, age 4; fibro-

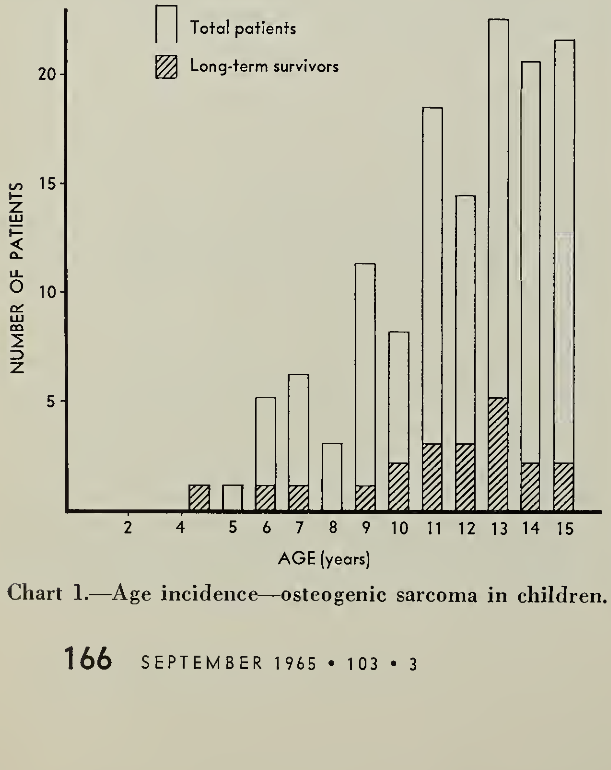

Chart 1.—Age incidence—osteogenic sarcoma in children.

TABLE 1.—*Osteogenic Sarcoma in Children—Site and Histologic Subgroup*—Asterisk (*) indicates Long-Term Survivors

Bone	*Total*	*	*Osteosarcoma*	*	*Chondrosarcoma*	*	*Fibrosarcoma*	*	*Parosteal Osteogenic*	*	*Secondary Irradiation*	*	*Secondary Chondrosarcoma*	*
Femur	75	13	62	6	6	2	4	2	3	3	0	0	0	0
Tibia	25	0	21	0	3	0	1	0	0	0	0	0	0	0
Humerus	16	4	11	3	2	0	2	1	0	0	1	0	0	0
Pelvis	3	0	0	0	2	0	0	0	0	0	0	0	0	0
Fibula	2	1	2	1	0	0	0	0	0	0	0	0	1	0
Mandible	2	0	1	0	0	0	1	0	0	0	0	0	0	0
Os calcis	2	1	0	0	2	1	0	0	0	0	0	0	0	0
Miscellaneous	5	2	0	0	0	0	0	0	0	0	0	0	0	0
Ulna	1	1	0	0	1	1	0	0	0	0	0	0	0	0
Scapula	1	1	0	0	0	0	0	0	1	1	0	0	0	0
Skull	1	0	0	0	0	0	0	0	0	0	1	0	0	0
Rib	1	0	1	0	0	0	0	0	0	0	0	0	0	0
Vertebra	1	0	1	0	0	0	0	0	0	0	0	0	0	0

COMPARISON OF LONG-TERM SURVIVAL* IN ADULTS AND CHILDREN

Totals—	Total	Osteosarcoma	Chondrosarcoma	Fibrosarcoma	Parosteal Osteogenic	Secondary Irradiation	Secondary Chondrosarcoma
Children	* 21 of 130 (16.2%)	* 10 of 99 (10%)	* 4 of 16 (25%)	* 3 of 8 (37.5%)	* 4 of 4 (100%)	* 0 of 2	* 0 of 1
Adults	* 77 of 422 (18.1%)	* 18 of 159 (11.1%)	* 26 of 123 (21.1%)	* 9 of 52 (17.4%)	* 13 of 18 (72%)	* 4 of 20 (20%)	* 5 of 11 (45.5%)

sarcoma, age 7; chondrosarcoma, age 9; osteogenic sarcoma arising in irradiated bone, age 9; secondary chondrosarcoma, age 11; parosteal osteogenic sarcoma, age 12. Male and female patients were in equal number.

Site

Most (91.5 per cent) of the neoplasms in this series originated in the long bones, and 83 per cent of these extremity tumors arose in the metaphyseal region (Chart 2). The lower extremity contained 80 per cent and the upper extremity 13 per cent. Only 7 per cent of the tumors were at sites other than an extremity. Sixty per cent were located about the knee.

Ninety per cent of all tumors were at three osseous sites—femur, tibia and humerus. More than half (75) of the total number of tumors were located in the femur (3 proximal, 13 diaphysial, 59 distal). There were 25 tumors in the tibia (19 proximal, 3 diaphysial, and 3 distal) and 16 in the humerus (13 proximal, 3 diaphysial).

Signs and Symptoms

Pain was the initial and most distressing symptom in 75 per cent of cases. A swelling was the first symptom in 15 per cent. A third and infrequent initial symptom was a disability such as limping or restriction of motion. Persistent pain, swelling or both demand roentgenographic examination of the affected bone. A fracture was the presenting symptom in two patients and later occurred in 17.

The average time from the first symptom to diagnosis was three months with a median of two months and a range of from less than 1 to 24 months. Only seven children had symptoms for more than six months before treatment was begun.

A swelling was the commonest (90 per cent) finding on physical examination. Redness, point tenderness, increased local heat and limitation of joint motion were noted in half of the patients.

Trauma

Several patients gave a history of minor trauma to the involved area. (We believe that the injury directed the patient's attention to a lesion already present.)

Laboratory Studies

Serum alkaline phosphatase is the only laboratory determination which may be significantly altered in patients with osteogenic sarcoma. Of 98 patients initially tested, 23 had elevated levels (more than 15 Bodansky units in children). Of 75 patients with normal values when sarcoma was first diagnosed, five had later elevations. Two of the 21 with long-term survival had high serum alkaline phosphatase before treatment (18.3 and 20 Bodansky units) and in these cases the level reverted to normal after therapy. Only nine children had alkaline phosphatase values greater than 30 Bodansky units terminally, ranging from 31.4 to 95.4.

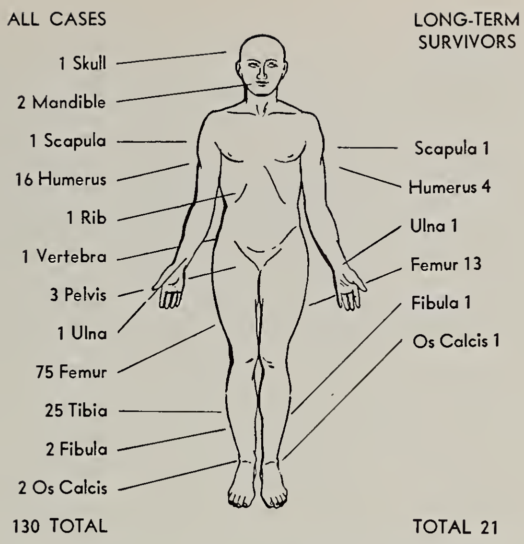

Chart 2.—Location of osteogenic sarcoma in children.

In our experience the frequency of alkaline phosphatase elevations and the range of abnormal values associated with osteogenic sarcoma are about the same for children as for adults, with the exception that sarcomas arising in bone affected by Paget's disease occur only in adults and in these patients there is usually pronounced elevations of serum alkaline phosphatase.

Associated Conditions

Pathogenesis and the cause of osteogenic sarcoma remain unexplained and in only three cases in this series of children did the lesion originate in bone altered by preexisting disease or previous treatment. Two children had received radiation therapy, one for a neuroblastoma and the other for a humeral bone cyst, and in both cases an osteogenic sarcoma developed in the treated bone, six years later in one case, eight years in the other. In another case, that of a boy with multiple osteochondromas since age 4, a secondary chondrosarcoma developed in one osteochondroma at age 11.

Metastasis

Pulmonary metastasis was demonstrated roentgenographically at the time of admission in 13 per cent of the children in this series. X-ray films of the chest are therefore mandatory in all cases before definitive treatment is begun. Metastatic lesions in the lungs were demonstrated in at least 91 per cent of patients at the time of death, and most of these patients died of respiratory failure.

Metastasis to bone was rarely apparent (1 per cent) when the diagnosis of sarcoma was first established, but such lesions were identified later in 25 per cent of patients who died of sarcoma.

Other sites of metastasis, such as lymph nodes, soft tissue, heart, brain and ovary were noted in 9 per cent of patients who died of sarcoma.

Sequellae of metastasis included paraplegia in five patients with vertebral metastasis and pneumothorax in one patient with pulmonary metastasis.

Treatment

One hundred and three children were treated surgically with curative intent and in all but two cases amputation was eventually carried out. Fifty-four (52.5 per cent) of the surgically treated patients received preoperative irradiation from various sources—radium element packs (in the years 1925-1936), orthovoltage (1928-1955) and supervoltage (1947-1955). A tumor dose varying from 1,500 to 12,000 rads was complemented by surgical ablation one day to many months after completion of radiation therapy. Nine children were treated solely by radiotherapy. Eighteen children with distant metastasis received only palliative therapy.

Surgical ablation is the only curative therapy for a skeletogenic sarcoma. An extremity tumor should be amputated by removing the entire bone and sufficient soft tissue to minimize the liability of recurrence. For sarcoma of bone in non-extremity locations, radical excision of the affected bone and the surrounding soft tissue is recommended.

Palliative therapy of a bone sarcoma is rarely indicated when pulmonary or osseous metastatic lesions are present. Severe pain may be lessened by irradiation and occasionally amputation may be justified for an ununited fracture or a massive tumefaction.

Irradiation as the sole method of therapy was never curative; preoperative radiation therapy has been advocated by some clinicians, but no evidence was found in the present series to support this recommendation.

Survival

The absolute survival for the entire series of 130 osteogenic sarcomas was 18.5 per cent at five years and 16.2 per cent at 10 years. Only one patient was lost to follow-up, and for statistical purposes was presumed dead as a result of sarcoma.

Of the 103 patients surgically treated, one died in the postoperative period. Twenty-four children (23.3 per cent) were alive at five years and 21 (20.4 per cent) were alive at 10 years. Six patients were alive and well more than 20 years after treatment. Of those who died of sarcoma, none died more than seven years after diagnosis.

All of the long-term survivors had had amputation. In six cases in which conservative surgical excision was employed, there was local recurrence of sarcoma; then in three of those cases in which the tumors were in an extremity, amputation was done and two of the children then had long survival without recurrence. The three patients with non-extremity tumors (two mandible, one ilium) were retreated by reexcision (one to three times) unsuccessfully.

Radiation therapy brought about no "cures" when used as the only treatment. Survival after irradiation ranged from three months to 26 months after diagnosis, with an average and median interval of 12 months.

Treatment failures were more frequent in patients receiving preoperative irradiation and amputation than in patients treated solely by amputation. Of 47 patients who were treated primarily by amputation, 15 (32 per cent) were alive at five years, and 12 (25 per cent) were alive at 10 years. Of 54 children who first had radiation therapy and then amputation, nine (16.7 per cent) were alive at both five and 10 years after diagnosis. The median survival time for children in whom treatment failed was 14 months when the treatment was amputation alone, and 11 months when it was irradiation and amputation.

Survival was higher when the sarcomas were in peripheral locations such as the long bones than when they were at other skeletal sites, such as the skull, vertebrae and ribs where radical operation cannot be done. No long-term survivals were noted for skeletogenic sarcoma in the following locations: Tibia, pelvis, mandible, skull, rib or vertebra. The osseous sites of sarcoma in the 21 cases in which there was long-term survival were as follows: Femur, 13 (12 distal, 1 diaphysial); humerus, 4 (3 proximal, 1 diaphysial); and one each in the fibula, ulna, scapula and os calcis.

The single most important factor in prognosis in children with a skeletogenic sarcoma was the histologic type (Table 1). The majority of tumors in this series were osteosarcomas and the long-term survival associated with them was the poorest (10 per cent). The survivals in the other three primary subgroups were as follows: Chondrosarcoma, 25 per cent; fibrosarcoma, 37 per cent; parosteal osteogenic sarcoma, 100 per cent. These absolute survival rates in children are nearly identical with the end-results in adults with osteogenic sarcoma (Table 1).

A thoracotomy was performed in two patients with unilateral lung metastasis. One patient was alive and well at last report, 15 years after lobectomy and 20 years after the diagnosis of fibrosarcoma of the proximal humerus (excised four times before amputation). The other patient died with sarcoma three years after lobectomy and six years after disarticulation of the hip joint for an osteosarcoma of the femur.

Osteosarcoma in Children and in Adults

Seventy-five per cent of the skeletogenic sarcomas in the children in the present series were classified as osteosarcoma. This is twice the proportional incidence of osteosarcoma in adults (37.5 per cent) and may be explained in part by an older average age of patients with chondrosarcoma and fibrosarcoma and the absence of Paget's sarcoma in children. In addition, few sarcomas in children were located in the head and trunk. At these sites chondrosarcoma is more frequently encountered, and this histologic subgroup is less common in children than in adults.

Prognosis can be related to the tumor size—the smaller the sarcoma, the more favorable the prognosis—both in children and in adults. In this series of 99 osteosarcomas, there were only two sarcomas 5 cm or less in size and in both these cases long-term survival was brought about by operation. In none of the cases in which the lesions were more than 15 cm in diameter was long-term survival achieved. Grading of the tumors according to Broders' method was not useful in prognosis in osteosarcoma, either in children or in adults.

Definitive treatment, consisting of biopsy followed by amputation within one month, without interval resection or irradiation, resulted in a 16 per cent five-year survival and a 13 per cent long-term survival for osteosarcoma in children. These end results are similar to those observed in our experience with adults.

In other parameters of comparison, no essential differences between children and adults were noted. The local recurrence rate ranged from 15 to 20 per cent for extremity tumors and 85 to 100 per cent for sarcomas in an axial location. The incidence of late failures (death due to sarcoma more than five years after diagnosis) was similar (2 to 4 per cent) for children and adults with osteosarcoma.

Comment

In light of the long-term survival rate for osteogenic sarcoma in children achieved by radical ablative surgical operation—23 per cent at five years and 20 per cent at 10 years—the often expressed opinion that prognosis is extremely poor in young people with osteogenic sarcoma cannot be accepted. Pessimism should never influence a therapeutic decision in favor of irradiation in lieu of radical ablative operation. A delay of definitive surgical treatment to permit preoperative irradiation is not justified by the end results in this series.

Children and adults should be treated similarly for osteogenic sarcoma. This study has revealed no dissimilarity in the end results of treatment relative to age. There is a difference, however, in the incidence of the histologic subgroups in children and adults.

The psychological trauma of amputation is far greater for the parent than for the child; it has been our experience that children will readily accept the decision for amputation and can be easily rehabilitated as amputees. Whatever fleeting comfort the parents may get from a recommendation for conservative resection or irradiation must be measured against the knowledge that it is at the expense of depriving the child of one chance in five of "cure."

The findings which we have reported are similar in most respects to those in a series of 129 osteogenic sarcomas (*osteosarcoma* in our nomenclature) in children at the Mayo clinic reported by Hayles and coworkers.[4] They reported one patient with osteosarcoma treated only by radiation therapy to be alive and well for 34 years. We had no "cure" by irradiation; although we at first thought we might have, on pathologic review the lesion was reclassified as a chondroblastoma. There is no apparent explanation for the pronounced dissimilarity between the Mayo series and ours in the survival rate of patients with tibial sarcomas. In the Mayo series the survival rate associated with lesions at that site was better than average (40 per cent) whereas we had no survivors. Also, the Mayo group considered histologic grading of osteosarcoma to be useful in prognosis, and in our experience it was not.

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Late Intestinal Obstruction in Patients Surviving Neonatal Meconium Ileus

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■ *Two of 15 children who survived neonatal meconium ileus had "meconium ileus equivalent." They were treated with hydration, pancreatic enzyme therapy and antibiotics. One of these children died from pulmonary disease at the time of the bowel obstruction.*

The survival rate of infants with meconium ileus is steadily improving because of prompt operative intervention, better preoperative and postoperative care and long-term treatment with enzyme supplements and antibiotics. Late intestinal obstruction due to adhesive bands, volvulus, intussusception or "meconium ileus equivalent" may occur in children previously treated for meconium ileus of infancy.

The omission of pancreatic enzyme supplementation and the occurrence of respiratory infections are frequently associated with "meconium ileus equivalent."

In this series of patients four of the infants treated surgically for neonatal meconium ileus died in the early postoperative period.

MECONIUM ILEUS occurs in 5 to 15 per cent of infants with cystic fibrosis.[4,5,15,20] It has been reported as being the cause of intestinal obstruction in up to 20 per cent of the cases in several large series of patients with cystic fibrosis treated for intestinal obstruction.[4,14,17] Since the successful surgical treatment of meconium ileus reported by Hiatt and Wilson in 1948,[10] more and more infants with this complication of cystic fibrosis are surviving the neonatal period.

Clinical Material

A study was made of the early mortality and incidence of late intestinal obstruction in 19 cases of meconium ileus which occurred in a group of 250 children with cystic fibrosis admitted to the University of California Medical Center, San Francisco, between 1942 and 1964.

Four patients with meconium ileus were treated successfully without operation; 14 were operated upon. One patient died before operation was possible. Five infants were operated upon in other hospitals. Three of the patients required reopera-

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TABLE 1.—*Data on Infants with Meconium Ileus and Cystic Fibrosis, University of California Medical Center, San Francisco, 1942 to 1964*

Case No.	*Sex*	*Treatment*	*Result*
1	F	Hydration and enemas.	Intestinal obstruction due to inspissated fecal matter at 16 months of age. Well when last seen at 3 years of age.
2	M	Detorsion of midgut volvulus at 3 days of age.	Died at 6 years of age from respiratory failure.
3	M	None. (Passed "plug" spontaneously on fifth day of life.)	Well at 8 years of age.
4	F	Detorsion of midgut volvulus at 4 days of age.	Well at 15 years of age.
5	F	Hydration and enemas.	"Dilatation of the esophagus" demonstrated radiographically when last seen at 4 months of age.
6	F	Celiotomy and intravenous hyaluronidase at 2 days of age.	2 later episodes of intestinal obstruction at 5 and 12 years of age. Died during second episode from pulmonary insufficiency.
7	M	Hydration. Spontaneous evacuation of stool.	Well at 4 years of age.
8	F	Detorsion of midgut volvulus and irrigation of distal bowel at 2 days of age.	Died from pulmonary insufficiency at 8 years of age.
9	F	Celiotomy at 2 days of age. Irrigation of distal bowel with pancreatic enzyme solution.	Died from pneumonia and accompanying ileus at 2 months of age.
10	F	Operation (type unknown) performed at 2 days of age.	Reoperation for persistent obstruction on fifth day of life. Well at 14 months of age.
11	F	Ileostomy on first day of life.	Ileostomy closed after one week. Well at 3 years of age.
12	M	Enterotomy and detorsion of volvulus.	Reoperation 46 days later for persistent incomplete intestinal obstruction. Died one day later from the effects of long-standing malnutrition.
13	M	Detorsion of volvulus at 2 days of age.	Reoperation 4 days later with resection of jejunum and detorsion of volvulus. Died of peritonitis on seventh day after birth.
14	F	Enterotomy and evacuation of stool second day of life.	Associated cleft palate. Died at 2½ months of age from pulmonary insufficiency.
15	M	Enterotomy on the first day of life.	Last seen at 1 year of age. (State of health not specified.)
16	F	Ileo-ileostomy at 2 days of age.	Well at 18 months of age.
17	M	Ileo-ascending colostomy on the first day of life.	Died 13 days later of pulmonary insufficiency. Examination revealed incomplete obstruction at the anastomosis.
18	M	Ileo-ileostomy at 2 days of age.	Intestinal obstruction at 18 months of age. Concomitant melena. Treated with enemas without operation. Died at 2 years of age from pulmonary insufficiency.
19	M	None.	Died in the first 24 hours of life before operation could be performed.

tion in the early postoperative period for persistent bowel obstruction.

Fifteen of the 19 infants with neonatal meconium ileus survived (Table 1). One patient (Case 19, Table 1) died less than 24 hours after birth, before operation could be performed. A second patient (Case 17) died from respiratory failure on the 13th postoperative day. One infant (Case 12) who had a second operation for chronic incomplete small-bowel obstruction, died after persistent anorexia, on the 49th day of life. Another infant (Case 13) who required reoperation for continuing obstruction died from peritonitis seven days after the original exploration.

Late Obstruction

Intestinal obstruction occurred later in three (Cases 1, 6, 18) of the 15 survivors of neonatal meconium ileus. In two cases the obstruction was due to inspissated feces (called "meconium ileus equivalent" by Pensen).[12] One of these children (Case 1) had not been operated upon in the neonatal period. The episode of intestinal obstruction followed an illness of one week, manifested by nausea, vomiting and an upper respiratory tract infection. One of the three patients (Case 6) had two episodes of obstruction after treatment of meconium ileus by celiotomy and enemas. The first episode, when she was five years old, responded to hydration and pancreatic enzyme supplements. During the second bout of obstruction, at the age of 12, the patient died from pulmonary insufficiency. On both occasions she had been receiving pancreatic granules before entering the hospital. The other child (Case 18) had only one episode of intestinal obstruction, which was demonstrated by barium enema and relieved by further enemas, suggesting the possibility of intussusception. Both patients who had "meconium ileus equivalent" (Cases 1 and 6) responded to treatment with pancreatic enzyme replacement and hydration. Another patient (Case 9) was put in hospital at the age of two months because of vomiting and abdominal distention. Abdominal roentgenograms showed gas-filled loops of small intestine, compatible with an ileus secondary to a pulmonary infection rather than mechanical intestinal obstruction. Treatment was unsuccessful and the patient died of pneumonia.

Only one of these children was receiving pancreatic enzyme supplementation at the time of the development of "meconium ileus equivalent." One (Case 18) had pneumonia, and the first patient in the series had an upper respiratory tract infection before the recurrent episode of intestinal obstruction.

Discussion

The survival rate of infants operated upon for neonatal meconium ileus has been improving steadily. In the present series the survival rate was 79 per cent. Successful treatment depends upon early diagnosis and careful supportive measures, including accurate intravenous fluid therapy and judicious surgical intervention. Pancreatic enzyme therapy, prophylactic administration of antibiotics and vigorous treatment of respiratory infections have also enhanced the survival rate.

Little has been reported on the late gastrointestinal problems of children who have had meconium ileus in infancy.[15-20] Some of these patients may have persistent steatorrhea and uncontrolled fecal losses of nutrients despite adequate medical management, and others may have "short bowel" or "blind loop" syndrome secondary to operative treatment. Still another group may have recurrent intestinal obstruction due to "meconium ileus equivalent" or other mechanical factors (intussusception, volvulus or adhesions).[3,8,12] Other infants initially treated by ileostomy may die because of abnormal loss of fluids and electrolytes.[2]

TABLE 2.—*Meconium Ileus. Review of Reported Cases*

Reported By	*No. Patients*	*No. Survivors*	*No. Patients Developing Late Obstruction*
Hiatt and Wilson[10]	8	5	No follow-up
Bodian[3]	18(3)[a]	6	0
Gross[7]	63(1)	22	1[b]
Thomsen[21]	5	2	No follow-up
Bettex[1]	14	1[c]	5
Wangensteen[22]	5(2)	2	No follow-up
Nixon[15, 16]	28	6	1
Clatworthy[4]	12	7	No follow-up
Santulli[18]	37	12	1
Fox[6]	12(1)	6	1
Herson[9]	17	6[d]	0
MacDonald[13]	27	9	1
Hill[11]	28	17	No follow-up
Graham and Jaffe (1964)	19(5)	15[e]	3
Totals	293	116	13

[a] Figure in parentheses indicates number of patients treated without operation or who died preoperatively.

[b] A later report (Shwachman,[19] 1956) describes two additional patients who developed "meconium ileus equivalent."

[c] Six infants lived 33 to 60 days; one was well at 9 months of age.

[d] One died at 2 months of age with pulmonary complications.

[e] Two additional patients failed to survive the first year of life.

In the present series, recurrent mechanical obstruction of the small bowel due to impaction with inspissated feces occured in 2 of the 15 patients surviving neonatal meconium ileus. One of these children died at the time of the second obstruction. In this study the incidence of late intestinal obstruction in infants who survived meconium ileus of the newborn was greater than in other reported series (Table 2). This apparently high incidence of late intestinal obstruction may possibly be explained by the lack of follow-up data in some of the other reported series and the small number of patients reported here. Although Bettex[1] reported five instances of secondary intestinal obstruction in 14 patients after the successful treatment of neonatal meconium ileus, only one of the patients survived the second operation.

Five of the six children with cystic fibrosis from the University of California Medical Center who have experienced "meconium ileus equivalent" had not been receiving supplementary pancreatic enzymes at the time obstruction developed, and three had upper respiratory tract infections. The use of pancreatic enzyme supplementation is important in the prevention of "meconium ileus equivalent." The combination of upper respiratory tract infections and the discontinuation of pancreatic supplementation are contributory to "meconium ileus equivalent."

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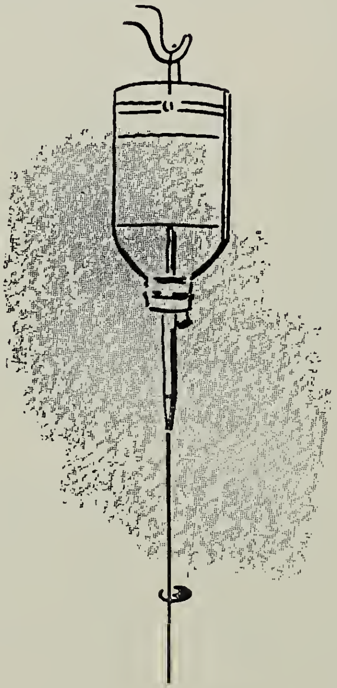

Don't Forget Morphology

The Importance of Evaluation of Blood Smears

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■ *A number of morphologic changes in the blood which may provide important diagnostic help, even in patients with normal blood counts, are frequently overlooked. Painstaking morphologic examination of a blood smear may at times lead directly to an important and unexpected diagnosis.*

DE GRUCHY[1] expressed a conviction of most hematologists when he stated that the examination of the blood smear is "the most important single investigation in the anemic patient." Many would add that the *skillful* examination of a *well-prepared* blood smear is one of the most important examinations in non-anemic patients as well.

The four non-anemic patients herewith reported had normal blood counts. In the blood of each, however, we found important morphologic abnormalities which less careful examination would not have detected. In each case the findings came as a surprise to the clinician and led to a diagnosis which he had not formerly suspected.

Reports of Cases

CASE 1. A 28-year-old man came to the laboratory for a complete blood count, and the results were entirely normal: (Hemoglobin 13.8 gm per 100 ml, packed cell volume 38 per cent, erythrocytes 4.22 million per cu mm, mean corpuscular volume 90 cubic microns, mean corpuscular hemoglobin concentration 36 per cent, leukocyte and differential counts normal). On examination of a blood smear, however, the technologist found unmistakable spherocytosis and polychromasia of the erythrocytes. We felt that in spite of the normal hemoglobin level, the findings suggested a spherocytic hemolytic process.

The patient had requested only a routine check-up, and a brief history and physical examination had demonstrated no abnormalities. On further questioning, however, he reported several bouts of so-called "hepatitis" over the years, one leaving him so anemic as to require four transfusions. Furthermore, his three children had become anemic and jaundiced shortly after birth, and two of them had received transfusions. Investigation for possible hemolytic disease of the newborn had demonstrated no blood group incompatibility between mother and babies. Unexplained anemia had persisted in all three since birth.

Further laboratory studies of the patient showed: (1) Much increased erythrocyte fragility in hypotonic saline solution (84 per cent hemolysis in 0.50 per cent sodium chloride; normal: 0 to 5 per cent); (2) negative direct antiglobulin test for adsorbed antibodies on the erythrocytes, using a broad spectrum antiglobulin serum; (3) normoblastic hyperplasia of the sternal marrow (granulocytes/erythroblasts = 1.07; normal: 2.5 to 6.0).

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When brought into the laboratory at our suggestion, the three children showed hemoglobin values of 10.8, 9.9 and 10.3 gm per 100 ml; in all three the erythrocytes showed definite spherocytosis and polychromasia. The patient's wife, in the third trimester of her fourth pregnancy, was not appreciably anemic (hemoglobin 11.5 gm per 100 ml), and her erythrocytes were morphologically normal. Although we used a battery of sensitive techniques, we could find no blood group incompatibility between the patient and his wife. She subsequently delivered a normal boy with 16.0 gms of hemoglobin per 100 ml, and normal serum bilirubin. A smear of the baby's blood showed no spherocytosis and only a normal amount of polychromasia. At last report, he remained well, without anemia or jaundice.

Comment: This patient and his first three children all had familial spherocytosis. In spite of many blood examinations in many different laboratories, and an apparent hemolytic crisis requiring transfusions, his disorder had escaped diagnosis. Likewise, no one had recognized the nature of the children's neonatal anemia and jaundice, in spite of a number of reports that familial spherocytosis may produce such changes. Morphologic examination of the blood smears had obviously not been performed with adequate skill and care.

CASE 2. A 61-year-old man came to the laboratory for a routine blood count, which proved entirely normal: (Hemoglobin 13.0 gm per 100 ml, leukocytes 9,550 per cu mm with normal differential count). The technologist, however, reported that, on examination of a blood smear, erythrocytes appeared large, and she found a few hypersegmented neutrophiles. Further studies confirmed the macrocytosis: (Packed cell volume 43 volumes per cent, erythrocytes 3.80 million per cu mm and mean corpuscular volume 114 cubic microns, as compared with a normal of 80 to 94). Despite the normal hemoglobin level, the hematologic findings suggested a megaloblastic disorder, presumably early.

The patient had gone to his physician for a general physical examination, which had shown apparently good health. Further questioning, however, elicited a history of recent indigestion and diarrhea, tiredness and a few pounds of weight loss.

Further laboratory studies demonstrated: (1) Megaloblastic sternal bone marrow; (2) abundant free hydrochloric acid in a fasting gastric specimen; (3) normal Schilling test of radioactive cyanocobalamin (vitamin B_{12}) absorption and excretion (16.3 per cent; normal: over 10 per cent); (4) excess fat in a single liquid stool specimen, but no parasites or ova; (5) an almost completely flat five-hour glucose tolerance curve (fasting: 106 gm per 100 ml; peak at one-half hour: 111 mg; low in three hours: 90 mg).

We diagnosed malabsorption syndrome with low grade folic acid deficiency. Treated with folic acid by mouth, the patient soon felt much improved, and the diarrhea cleared. Five months later, the hemoglobin level had risen to 15.1 gm per 100 ml, with a normal mean corpuscular volume of 93.5 cubic microns. The hypersegmented neutrophiles had disappeared.

Comment: The morphologic abnormalities seen on a blood smear from this non-anemic patient constituted the first recorded evidence of nontropical sprue, or malabsorption syndrome.

CASE 3. A 58-year-old rancher came to the laboratory for a complete blood count, which was within normal limits: (Hemoglobin 14.6 gm per 100 ml, leukocytes 9,600 per cu mm with a normal differential count). However, the technologist reported moderate polychromasia and heavy rouleaux of the red cells, and on further search found an occasional normoblast and a rare metamyelocyte and myelocyte. We interpreted these findings as suggestive of neoplastic disease of the bone marrow.

The patient had complained of an upper respiratory tract infection and increasing fatigue for three months. He had produced no bloody sputum but in recent weeks had lost 20 pounds. For many years he had smoked up to two packs of cigarettes a day. The only abnormalities found on physical examination had been a few rales at both lung bases posteriorly and slight prominence of the neck veins on the left.

X-ray films of the chest, however, showed an enlarged left hilus and segmental atalectasis extending into the left upper lobe. Bronchoscopic examination demonstrated virtually total occlusion of the left upper lobe bronchus. Small, hard, fixed lymph nodes, removed from the left scalenus fat pad, showed heavy infiltration with anaplastic bronchogenic carcinoma.

Comment: The first suggestion of malignant disease with bone marrow metastasis consisted of minimal morphologic changes in the blood at a time when the blood count remained normal. It would have been very easy to miss these changes, or to ignore them. Recognition of them proved of considerable diagnostic assistance to the clinician.

CASE 4. A 54-year-old woman visited a physician because of a progressive bruising tendency. On physical examination he found numerous bruises and petechiae scattered over the trunk and extremities. He could not feel the liver or spleen.

A study of the coagulation mechanism, the first laboratory procedures requested, demonstrated: (1) Adequate concentrations of the various plasma procoagulants; (2) a prolonged bleeding time (8½ min., Duke); (3) a decrease of platelets on the blood smears. As an incidental finding, the erythrocytes appeared quite large on the smears, with many target cells.

A complete blood count demonstrated a normal hemoglobin level but confirmed the findings of macrocytosis of the erythrocytes, and of thrombopenia: (Hemoglobin 13.2 gm per 100 ml, packed cell volume 37 volumes per cent, erythrocytes 3.58 million per cu mm, mean corpuscular volume 103 cubic microns, platelets 70,000 per cu mm as compared with a normal of 150,000 to 350,000). The leukocyte and differential counts were normal. Sternal marrow examination showed macronormoblastic hyperplasia and an abundance of megakaryocytes, with little evidence of platelet formation. Prussian blue stain demonstrated a moderate increase of marrow hemosiderin. The findings suggested cirrhosis with congestive splenopathy and hypersplenic thrombocytopenia.

A careful history at this time revealed that the patient had been jaundiced at birth, and again at age 27, following cholecystectomy. At age 50, a few weeks following transfusion for a pelvic operation, she had become deeply jaundiced and required several weeks to recover. She denied use of alcoholic beverages.

Liver function studies indicated severe impairment. A needle biopsy of the liver demonstrated portal cirrhosis with hemosiderosis.

The patient subsequently was severely ill and she died of hepatic failure less than two years after the first recognition of cirrhosis.

Comment: Macrocytosis of the erythrocytes, with target cells, observed at a time when the hemoglobin level was normal, constituted the first recognized sign of cirrhosis in this severely ill patient.

Discussion

Important morphologic findings often overlooked or misinterpreted on examination of the blood smear include: (1) Macrocytosis of the erythrocytes, particularly in the absence of anemia (Cases 2 and 4); (2) spherocytosis of the erythrocytes (Case 1); (3) elliptocytosis of the erythrocytes, often described meaninglessly as "anisocytosis and poikilocytosis"; (4) the microcytosis, target cells and basophilic stippling of thalassemia minor, often mistaken for iron deficiency; (5) thrombocytopenia or thrombocytosis, rarely recognized in the absence of a platelet count (Case 4); (6) heavy rouleaux, characteristically seen in multiple myeloma, macroglobulinemia, and in some malignant disease (Case 3); (7) the occasional young granulocytes and nucleated red cells often seen in malignant disease of the bone marrow (Case 3) and in myeloid metaplasia; (8) the primitive leukocytes of acute leukopenic leukemia. Each of these findings and a number of others have upon occasion led directly to an important and unexpected diagnosis.

Skill and care in the routine examination of blood smears pays occasional unexpected dividends in clinically useful information.

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Sialadenitis and Major Salivary Gland Tumors in Children

Experience at Los Angeles Childrens Hospital and a Review of the Literature

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■ *Except for mumps, the benign lesions most frequently seen in the salivary glands of a child are parotitis, hemangioendotheliomas and mixed tumors. Carcinoma and sarcoma are uncommon. Rapid growth and pain are features of malignant change.*

Chronic parotitis usually subsides under conservative treatment. If operation is necessary, total parotidectomy is advisable. Scout x-ray films and sialangiographic examination are useful in differentiating an inflammatory lesion from a neoplastic growth.

The treatment of choice for a non-inflammatory tumor is surgical excision, for most parotid tumors are radioresistant. Small masses should be completely excised for pathological evaluation. Since operation entails risk of damage to the seventh nerve, incisional biopsy may occasionally be indicated in the case of a large diffuse lesion for it is very likely to be benign and operation unnecessary. The risks of seventh nerve damage are magnified in a child as the anatomic structures are smaller and the nerve lies in a more superficial position.

On review of the records of 95 patients with major salivary gland problems admitted to the Los Angeles Childrens Hospital from 1948 to 1963 (Table 1), it was noted that except for obvious inflammation or infectious parotitis, the major reason for seeking medical attention was the presence of a non-tender, parotid lump or swelling.

Differentiating a neoplastic growth from chronic asymptomatic parotitis can be a difficult problem. For the most part, in the pediatric age group the lesions in the major salivary glands are of an acute or chronic inflammatory variety. They may be initially painless and grow slowly. Parotid tumors are seen in newborn babies and infants but are more common in older children. Salivary gland tumors can be found in aberrant locations—in the lips, the cheek, the palate and the floor of the mouth.

In children the leading cause of death under 14 years of age is accidents, but malignant disease leads in the five to nine year age bracket.[13] Rush and coworkers[16] noted that, excluding tumors of the brain and eye, more than 8 per cent of tumors in children are in the head and neck area, the most common sites being the skin, nasopharynx, thyroid and salivary glands. Lymphomas, neuroblastomas and reticuloendotheliosis are common secondary lesions in this region.

Reiquam[15] presented 20 cases of salivary gland tumors in children, 13 of which the lesions were hemangiomas. Howard[10] reported on 21 cases of parotid tumors in children and included five hemangioendotheliomas. He presented six cases of mixed tumor and on reviewing the literature from

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From the Los Angeles Childrens Hospital, Los Angeles.
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TABLE 1.—*Major Salivary Gland Disease in Children—Etiologic Findings in 95 Cases at Childrens Hospital, Los Angeles*

Mumps (excluded)	36
Chronic Parotitis	18
Acute Parotitis	24
Submaxillary Gland Sialadenitis	9
Tumors	4
Hemangiomas	4

1920 to 1949 noted that of 2,309 patients with mixed tumor only 66 were children. In 50 of the 66 cases the tumor was benign and in 11 cases malignant. Reiquam's review of 132 cases of papillary cystadenoma lymphomatosum showed only four cases in children. Twenty of the 132 lesions were benign, including 11 hemangioendotheliomas and six mixed tumors. Five of 14 carcinomas in the parotid were mucoepidermoid. Four undifferentiated carcinomas were noted and in children they appeared to be much more aggressive tumors than in the adults. Death from metastasis is most common from this tumor.

Byers and Ackerman[3] reported 24 cases of salivary gland tumors in children and 17 were mixed tumors. Bhaskar[1] reviewed 2,500 salivary gland tumors at the Armed Forces Institute of Pathology and found 27 cases in children. There were 22 juvenile hemangiomas, three lymphangiomas and two xanthomas. The Cancer Memorial Hospital experience in New York City[4] was limited in that only two of 233 pediatric head and neck tumors evaluated were tumors of the salivary gland.

Present Series

Parotitis.—There were 78 cases of parotitis seen at Childrens Hospital from 1948 to 1963. Thirty-six cases were diagnosed as mumps and the patients were discharged to the infectious disease ward at the Los Angeles County Hospital or to their homes. There were 18 cases of chronic parotitis, including three cases of tuberculosis, one of parotid cyst and one due to cat scratch fever. The cases of tuberculosis occurred in children two to three years of age. In only five of the cases of chronic parotitis was biopsy done and none of the patients had subtotal parotidectomy. The clinical course and the sialogram indicated conservative therapy with antibiotics and observation as the rule. The age span of onset was from seven months to 18 years. There was no predominant side of involvement, and in four cases both sides were involved. The most common symptom was an asymptomatic firm swelling which in several cases was recurrent. In all but one case the lesion subsided with time.

There were 24 cases of acute parotitis, of which two were postoperative. Two-thirds were in males, and the right side was involved twice as often as the left. Staphylococcus aureus was isolated in 10 cases, streptococcus in one and pneumococcus type III in another. One of the two patients with postoperative parotitis had had orchidopexy; and the other, who died four days after operation, had had pyloromyotomy for pyloric stenosis. Two of the 24 patients had a recent history of mumps. Nine infants had acute parotitis at one month of age or less, and two were affected at birth. The remainder were older. In nine cases incision and drainage was necessary because of fluctuation and pointing; and in four of the nine the patient was one month or less in age. No further therapy was required in any of this group. The common factor in the children less than one month of age appeared to be dehydration secondary to diarrhea, vomiting or other factors leading to dehydration or cachexia.

Hemangioma.—There were four cases of parotid hemangioma in the series, and in girls. In all cases the lesion was first detected at birth or within the first six months. One patient had had a parotid swelling since birth, with an overlying area of telangiectasia. A right subtotal parotidectomy was done at eight weeks of age with incomplete excision of the lesion. A persistent seventh nerve palsy was noted after operation. X-ray therapy was used at eight months of age and a 3 × 4 cm mass was still present when the patient was last observed at five years of age. In another case a parotid swelling developed when the child was five months of age, after an upper respiratory infection. The lesion was excised at 14 months of age without complication, recurrence or seventh nerve injury. The third child was treated conservatively for parotid hemangioma on the right side that had begun when the patient was less than one year of age. Ligation of the external carotid artery, radiation therapy and subsequent injection of sclerosing solutions were carried out. A 3 × 4 cm mass was still present at eight years of age and a resection was planned. The fourth case was in an eight-month-old white girl who had had red discoloration at the angle of the right jaw since birth. A mass that first appeared at six months of age grew to 4 × 6 cm within two months. Subtotal parotidectomy was done on October 11, 1963, with preservation of the facial nerve. The patient recovered without facial paralysis.

Submaxillary Gland.—Nine cases of submaxillary problems were reviewed. All of the lesions were of an inflammatory nature and no neoplastic growths were detected. Two sublingual gland cysts were marsupialized into the oral cavity. One 11-year-old child had a calculus removed from the Wharton's duct on the left. Three children had incision and drainage for a submaxillary abscess and two had excision of the gland for what appeared on sectioning to be an infectious granulomatous inflammation.

Parotid Neoplasms.—Four cases were reviewed. Abstracts of the records follow:

CASE 1. A six-year-old boy was admitted in January, 1961. A mass had been present in the right parotid gland for one month. Soon after admission the patient had total parotidectomy with sacrifice of the seventh nerve. The pathologist reported a malignant mixed tumor with neurofibrosarcoma as a major element. Microscopically there were elongated cells with fibrillar processes extending in various directions. There was a definite tendency to palisading. The nuclei were spindle shaped and vesicular. The patient was treated postoperatively in March, 1961, with 1,650 roentgens. He died at home in November, 1961, with extensive involvement of the face and oral cavity in neoplastic growth.

CASE 2. An eight-year-old white boy was admitted in October, 1951, with a three-week history of a 4 × 4 × 3 cm mass in the area of the right parotid gland. The tumor was resected, including the seventh nerve, and postoperative radiation was given. The pathologist reported a malignant mesenchymal tumor, probably in the nature of a neuroblastoma or neurosarcoma. The child subsequently received radiation therapy but died of extensive local disease on April 17, 1952.

CASE 3. A girl 18 months of age when first seen in July, 1946, had an irregular soft mass 1 cm in diameter that had been present since birth in the right parotid area. It was soft, movable and felt as if it contained many cysts. When she was five years of age, the tumor involved the right cheek and right ear. Several areas of skin pigmentation overlay the tumor. There were *cafe-au-lait* spots over the body. In 1949 a large portion of the mass was excised and the patient had facial palsy thereafter. The pathologist reported the lesion was a plexiform neurofibroma. In July, 1957, radical excision of the tumor of the cheek and neck was carried out, and at that time the tissue showed considerable variation in nuclear size with hyperchromatism. There was increased cellularity with frequent mitotic figures. In comparison with previous specimens, there was a definite transition to a sarcomatous pattern. Over the succeeding 10 years, excisions with plastic procedures were carried out at yearly intervals. When last seen at 17 years of age the patient was married, had a child and was free of disease.

CASE 4. The patient, a 15-year-old white girl, first noted a non-tender movable mass at the angle of the right mandible in July, 1957. It had not increased in size and was asymptomatic. On examination a 2 × 3 cm firm movable mass was felt below the right ear lobule without significant enlargement of adjacent lymph nodes. In February, 1958, subtotal parotidectomy on the right side was carried out. The facial nerve was not injured. The pathologist reported the mass to be a well encapsulated 2.5 × 2 × 1.5 cm nodule made up in part of large areas of loose myxomatous tissue. There were small nests of epithelial cells scattered throughout. The diagnosis was benign mixed tumor of the parotid gland. When the patient was last seen in December, 1963, there was no evidence of recurrence.

Differentiation of Inflammatory Lesions from Neoplasms

A common problem in managing parotid swellings in children is the differentiation of an inflammatory lesion from a neoplasm. Since operation entails considerable risk of injury to the seventh nerve, every effort should be made to make sure it is necessary.

An inflammatory process is obvious when tenderness, pain, swelling, erythema, fever, drainage of purulent material from Stensen's duct and systemic reactions such as debility or malaise are present. Acute parotitis is seen most frequently after infections about the head and neck after general infectious diseases with septicemia and pyemia, after dehydration and cachexia following operative procedures, and in the course of chronic parotitis. The most common offending organisms are staphylococci, streptococci and pneumococci. The treatment is conservative and consists of local hygienic measures, application of compresses and administration of specific antibiotics. Incision and drainage is a necessity if the course of the disease fluctuates widely, and it may be indicated if infection appears to be progressive.

In taking a history, care should be taken to determine whether the parotid swelling is the first such instance or is a recurrent flare-up of inflammation. The swelling in chronic parotitis usually subsides completely at the end of an attack, but there may be some persistent enlargement and a history of recurrences. The disease can recur at intervals of weeks to months, and the attacks last from days to weeks. It occurs more frequently in children than in adults but may be found at any age. Fever, when it occurs with chronic parotitis, is usually of a mild degree and there is usually little constitutional disturbance. Roentgenographic studies rarely show parotid calculi. Sialographic examination may help to establish a diagnosis.[19]

For sialangiography, after the child is sedated a small lacrimal canula is inserted into the Stenson duct orifice and about 0.5 ml of a warm solution of contrast medium (Lipiodol®) is injected slowly. In most cases the ductal system is normal, but sialangiectasis may be present as indicated by a beaded appearance similar to that noted in bronchiectasis (Figure 1). This is most often a primary or congenital lesion and is fairly diagnostic of chronic parotitis. A diseased gland will usually take more contrast material than a normal gland. A further value of this examination is that the films may show any intraglandular or extraparotid growth that is causing pressure on the ductal system.

Etiology and Treatment of Chronic Parotitis

The cause of chronic parotitis in children is not known but infection secondary to a ductal obstruction is thought to be a common etiologic factor. Poor oral or general conditions, mucosal atrophy and glandular abnormalities are all involved. The gland may be involved as part of a secondary process from a generalized disease, as in sarcoid, lymphoma or tuberculosis. In children allergic disease and sensitivity to drugs have been incriminated.[14] Some of the drugs which may cause parotitis are mercury, lead, copper, iodine, nicotine and opium. Among food substances, spinach, pork, lemons, grapes, oranges, acidic foods, iodized salt and tuna fish have been inculpated.[2]

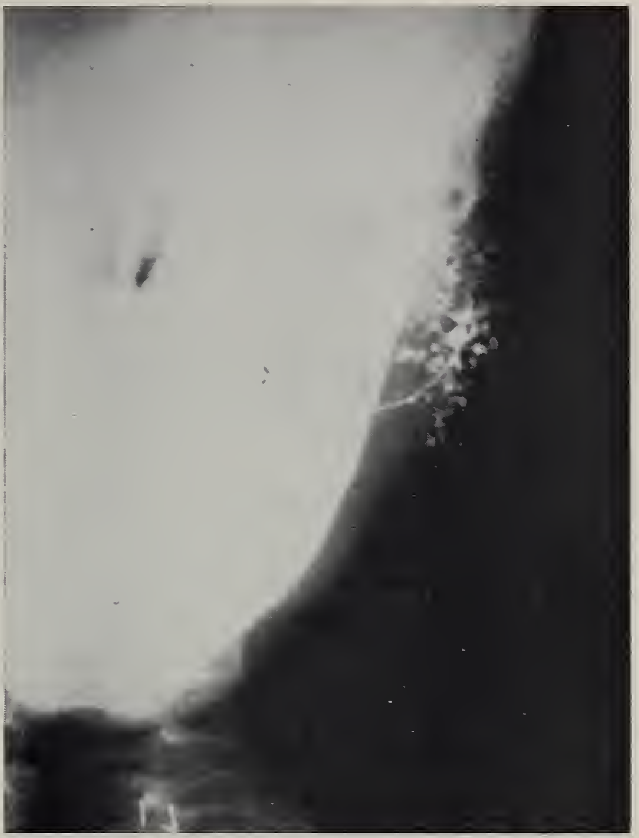

Figure 1.—Sialogram showing classic sialangiectasis in a seven-year-old boy who had chronic parotitis on the left side.

Dorrance[5] put emphasis on conservative management of chronic parotitis. In the majority of cases the disease subsides without operation. However, if severe disability and frequent attacks indicate operation, total parotidectomy is advisable.[6,15] Perineural adhesions are commonly encountered and the task of dissection is a painstaking one. If the deep lobe is left behind, salivary fistulas may occur or parotitis recur. Seventh nerve dissection is extremely hazardous should a secondary procedure become necessary.

One point to be emphasized with regard to parotidectomy in infants is that the mastoid process is not completely pneumatized and the stylomastoid foramen is in an unprotected and exposed position on the lateral skull surface. The nerve is only 0.5 mm in diameter, lies nearer the surface than in adults and can be easily injured.

Radiation therapy has been advised. However, it is difficult to destroy infectious activity in the parotid radiation. Furthermore, if it is used the mucous membranes of the soft palate, the mouth and pharynx will atrophy and the drying may be more uncomfortable than the parotid problem.[8]

In conservative management, oral and dental hygiene with mouth washes, passive massage, compresses and specific antibiotics are all worth trying. Small doses of roentgen therapy may help, although the hazard of giving radiation therapy in the head and neck area of a child is well documented.

Needle or incisional biopsy is advised for a diffuse asymptomatic lesion if after complete clinical and radiographic evaluation the diagnosis is still not established. The tissue obtained can be used for culture and microscopic examination.

Non-Inflammatory Tumors

The specific type of each of the following non-inflammatory tumors, as determined by examination of tissue, decrees the method of management:

Hemangiomas.—Hemangioma is the most common vascular tumor in children and it usually appears in the first year of life. Parotid hemangioma is more frequent in girls than in boys and in Caucasians than in persons of other races. It may show a transient increase in size during crying or straining, and when palpated may feel soft to firm. A bluish discoloration to the skin may be evident, this symptom depending on the amount of cavernous component present. Most tumors of this order are capillary hemangiomas without a true capsule. They tend to be lobulated.

Microscopically one sees solid sheets and masses of cells and anastomosing capillaries replacing parotid acinar structures leaving widely separated ducts. Silver stains for reticulum demonstrate the epithelial nature of the cells in the solid areas,[12] distinguishing it from a hemangiopericytoma, as the latter occurs entirely outside the reticulum sheet of the vessels.[17] The two common features are the formation of atypical epithelial cells in greater numbers than are required to line the vessels with a simple epithelial membrane, and the formation of vascular tubes with a delicate framework of reticulum fibers. The linings of the tubes have a decided tendency to anastomosis. Sialograms may show a distorted duct pattern. Malignant change is extremely rare.

Many kinds of therapy have been reported, including surgical excision, massage, radiation, implantation of radon seeds, use of sclerosing agents, carbon dioxide snow and ligature of external carotid artery. In some cases no treatment is given but the patient is kept under observation. There is no report of a complete spontaneous regression of a parotid hemangioma. If delay is possible, surgical treatment should not be carried out until the patient is at least six months of age. Rapid growth and recurrence have been observed in infants operated upon when younger. There is a tendency as the patient gets older for the tumor to have a capillary pattern and less cellularity and mitoses, this change being associated with a slower growth potential.[18]

As to the hazards of parotidectomy, Wolfe[20] in a review of the literature recorded 4 per cent mortality (two of 46 patients) and facial nerve injury in 25 per cent of cases.

Lymphangiomas.[1,9]—Lymphangiomas are uncommon in the parotid gland except by extension from the cervical area. Rare cases have been presented in which the tumor was confined to the parotid gland due to sequestered intraparotid lymphatic anlagen. Lymphangiomas are multiloculated and composed of cystic spaces of varying size. Microscopically the cysts are composed of randomly arranged intracommunicating and dilated lymphatic channels with a flattened epithelial lining of the walls. The lesions are usually slow-growing, but rapid enlargement may follow an upper respiratory tract infection. Surgical operation is considered the treatment of choice. Radiation and radon seeds are of doubtful value

Benign Mixed Tumors

Mixed tumors are common in adults, infrequent in children. Of a total of 2,309 cases of mixed tumor reviewed by Howard,[10] only 66 (less than 3 per cent) were in children. Many of these tumors are contained in a thin delicate capsule consisting of connective tissue and remnants of compressed salivary gland tissue. In reviewing the history of cases in which there was recurrence, it was noted that in almost 80 per cent of them the tumor had been broken into at time of operation. These tumors can be round, smooth and movable or nodular and fixed and the most frequent location is the tail of the parotid gland beneath the lobule of the ear. The size varies from 4 mm to 10 cm. Histologic examination often reveals excrescences 1 mm or less in diameter which jut through the capsule. This explains the presence of multiple local recurrences. When seen primarily the mass is usually solitary; lesions of recurrence are usually multiple. It has been noted that the recurrence rate after removal of mixed tumor is in the neighborhood of 20 or 30 per cent.

The growth rate of these tumors is variable. They may remain static as a painless lump for long periods or they may rapidly increase in size. Local pressure may cause discomfort or pain. Not often if the lesion is benign is there involvement of the seventh nerve. Ninety per cent of them are in the parotid gland, about 10 per cent are in the submaxillary gland and less than 1 per cent in the sublingual gland. The median age of patients is 42 years. One case was reported at birth. There are no familial tendencies and no etiologic clues. X-ray has little therapeutic effect. Cut surfaces of these lesions are an homogeneous grey-white. About 30 or 40 per cent contain some cartilage and various mucinous material. Recurrences can appear as long as 10 years later. In one case in the present series (Case 4) the growth was detected when the patient was 14 years of age. At the time of last report, six years after resection, there was no recurrence.

Malignant Mixed Tumors

In the case of malignant mixed tumors of the parotid area (which are uncommon in children) there is usually a history of a mass that has remained static or indolent for a long time, then has grown rapidly. These lesions are usually larger than benign tumors in the same area and they are usually fixed either to the deeper structures or to the skin. They may be partially encapsulated. Sectioned surfaces appear mushy and friable rather than tough and resilient. The malignant change can be carcinomatous or sarcomatous. Seventh nerve involvement is not common but does occur. Pain is a frequent symptom. The recurrence rate after excision is about 50 per cent. Metastasis to lungs, bones, abdominal viscera and brain has been noted.

For removal, an incision giving adequate exposure is necessary in order that the tumor may be excised with good margins and without spilling the contents. Salivary fistulas occur infrequently and are usually temporary. There was one malignant mixed tumor in our series, in a six-year-old boy (Case 1).

As far as carcinomas in general are concerned, the most common in children, as in adults, is the muco-epidermoid carcinoma. In about one-third of the patients, the tumors persist or recur. Undifferentiated carcinoma is the second most frequent variety in children and it is the most malignant of the juvenile carcinomas in the parotid area.

Although sarcomas are rare, there were two cases in the present series, one case of malignant parotid mesenchymal tumor and one of parotid plexiform neurofibroma with sarcomatous change (Cases 2 and 3).

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REVIEW ARTICLE

The Immunoglobulins

With Special Reference to Macroglobulins and Macroglobulinemia

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THE SERUM contains many proteins, including a highly complex group known as the gamma globulins. Because antibodies in man and animals are associated mainly, and possibly exclusively, with these proteins, the gamma globulins are also referred to as immunoglobulins. Certain other proteins with similar chemical and antigenic characteristics but with no known antibody function are chemically related to the immunoglobulins. Principal among these are the Bence Jones proteins and the myeloma proteins.

The immunoglobulins of normal serum are heterogeneous. Although they have certain properties in common, they differ in a number of respects, including sedimentation characteristics, molecular size, electrophoretic and immunologic properties and carbohydrate content. In recent years the immunoglobulins have been divided into three major groups on the basis of physical, chemical and immunologic criteria and described in terms appropriate to each (Table 1). This review describes in brief the classification and nomenclature of the immunoglobulins according to these criteria and collates recently acquired data on these proteins in normal and hypergammaglobulinemic states.

Properties of the Immunoglobulins

Molecular size.[30] About 70 per cent of the gamma globulins of normal serum consists of components of low molecular weight, about 160,000. By analytical ultracentrifugation, these molecules have a sedimentation coefficient (S) of 7 Svedberg units; hence they are termed the 7S gamma globulins. A second group, comprising about 5 to 10 per cent of the total, consists of heavier components, with a molecular weight of 1,000,000 and S rates ranging from about 17 to 20. These proteins are referred to in general as the 19S components or macroglobulins. In both normal and pathologic sera, from 15 to 20 per cent of the total macroglobulins have higher sedimentation rates (27 and 32S) (Figure 1) and at present are considered to be polymers of the 19S gamma globulins. Recent immunologic studies, however, have indicated antigenic differences between these proteins and the 19S component.[56] An intermediate group of gamma globulins, constituting about 20 to 25 per cent of all gamma globulins, has also been identified. These proteins, which range from 7 to 17S,[51] with the 7S component predominating, differ antigenically from the 7S and 19S gamma globulins.

Electrophoretic mobility. By electrophoresis, the globulin fraction of serum separates into subfractions, each of which migrates toward the anode of the electrophoretic apparatus at a characteristic rate. The route of migration has been arbi-

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TABLE 1.—*Physical, Chemical and Immunologic Properties of the Three Immunoglobulins of Normal Serum*

Immunoglobulin[*]	*Normal Serum Concentration gm per 100 ml*	*Molecular Weight*	*Sedimentation Rate*	*Electrophoretic Mobility*	*Carbohydrate Content Per Cent*	*Polypeptide Chains*	*Genetic Determinant*
γ_2 (γ_{ss}; γ_G)	1.0	160,000	7S	gamma zone	2	L[†] Hγ_2	Inv Gm
γ_{1A} (β_{2A}; γ_A)	0.1-0.2	160,000 to 500,000	7S to 17S	mid-gamma into beta zone	10	L[†] Hγ_{1A}	Inv
γ_{1M} (β_{2M}; γ_M)	0.1	1,000,000 or greater	19S	mid-gamma into beta zone	10	L[†] Hγ_{1M}	Inv

[*] Alternative terms are given in parentheses; γ_G, γ_A and γ_M are the terms proposed in 1964 at the WHO Meeting on the Nomenclature of Human Immunoglobulins in Prague (Bull. Wld. Hlth. Org. 30:447-450, 1964).

[†] Type I and II.

trarily divided into zones, designated alpha, beta and gamma in order of decreasing mobility. At the end of the electrophoretic run, the subfractions can be identified by the distance they have traveled and by their characteristic position in a particular zone.

The 7S components of normal serum have a wide range of electrophoretic mobility, but migrate mainly in the gamma zone. The 19S components can be separated electrophoretically into two types of protein, one migrating principally in the gamma zone and the other migrating in the alpha$_2$ subzone. The α_2-globulins, which constitute about two-thirds of the total macroglobulins in normal serum, have no known antibody activity and are not considered to be immunoglobulins. The two types of macroglobulin migrate in the described zones in free electrophoresis and in zone electrophoresis in a variety of media, including filter paper,[10] starch block and agar gel. In gels of hydrolyzed starch[48] or of polyacrylamide, the α_2-globulins retain their characteristic mobility, but the γ-macroglobulins fail to penetrate the gel. The inability of the γ-macroglobulins to enter the gel provides a useful laboratory tool for differentiating between multiple myeloma and Waldenström's macroglobulinemia.

Immunoelectrophoretic mobility. Immunoelec-

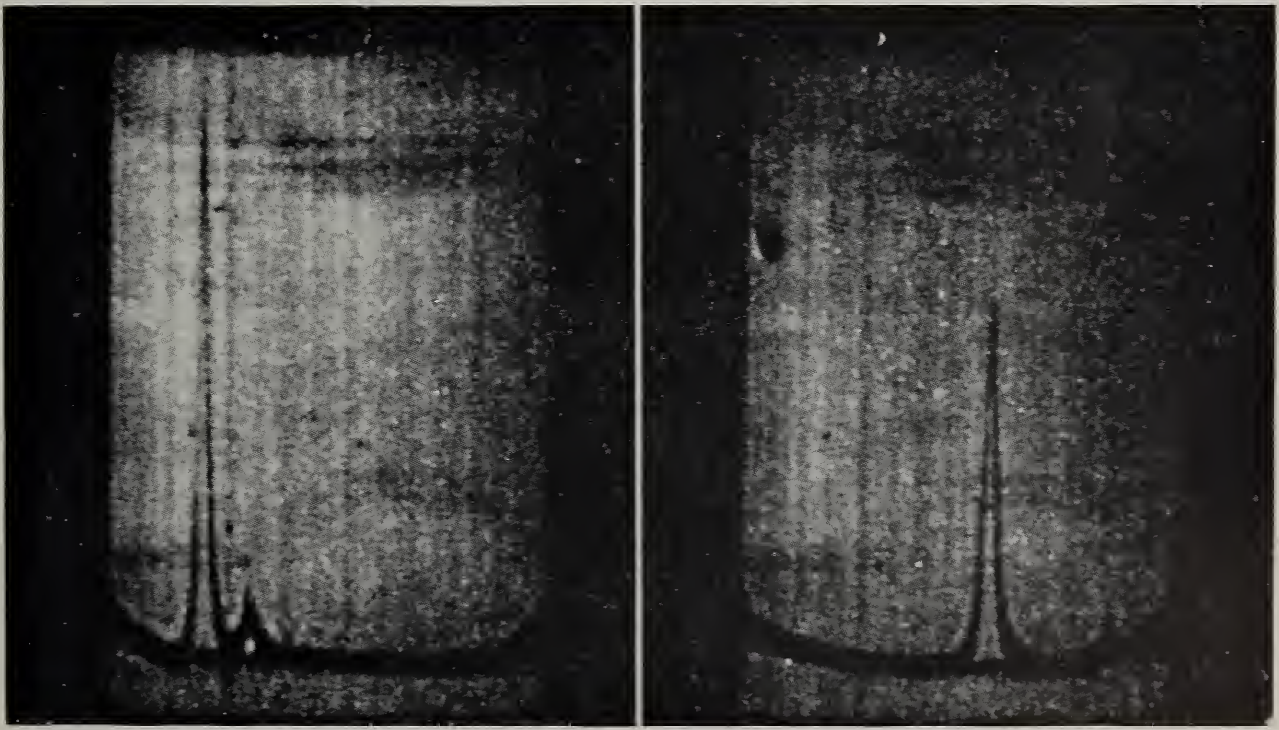

Figure 1.—Ultracentrifugal (59,780 rpm) pattern of a purified pathologic macroglobulin at 16 minutes (left) and at 40 minutes (right). Direction of sedimentation is from left to right. The small peak to the right of the 19S peak is a higher S rate polymer.

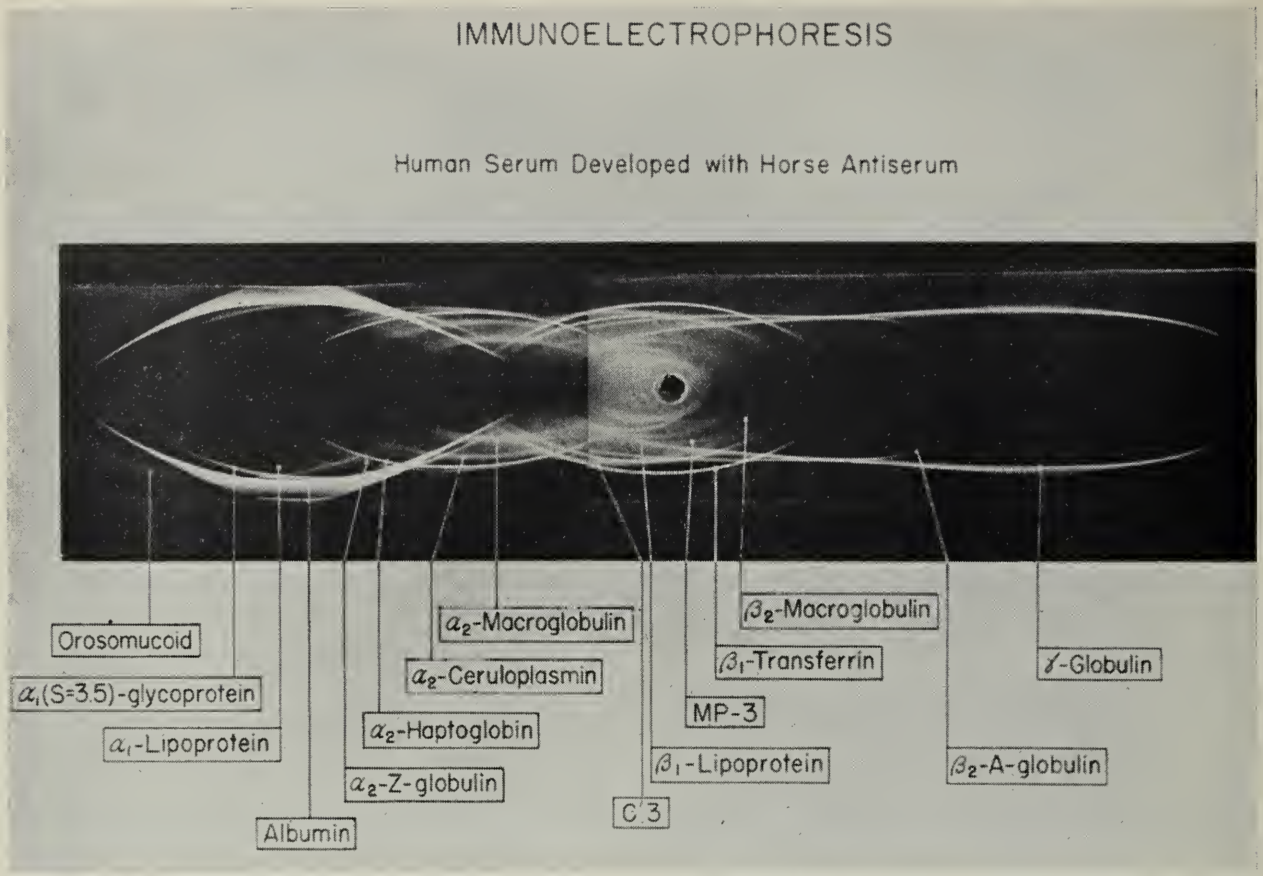
IMMUNOELECTROPHORESIS
Human Serum Developed with Horse Antiserum
Orosomucoid
α_1(S=3.5)-glycoprotein
α_1-Lipoprotein
Albumin
α_2-Z-globulin
α_2-Haptoglobin
α_2-Ceruloplasmin
α_2-Macroglobulin
C3
β_1-Lipoprotein
MP-3
β_1-Transferrin
β_2-Macroglobulin
β_2-A-globulin
γ-Globulin

Figure 2.—Immunoelectrophoretic pattern of normal serum, demonstrating the many components that can be identified by this procedure.

trophoresis, a relatively recent technique, makes use of the diffusion, electrophoretic, and immunologic properties of the serum proteins. With this procedure, a sample of serum or protein is first separated into fractions by electrophoresis, usually in agar gel under standard conditions. A trough is then cut in the supporting medium, parallel to the line of migration, and is filled with rabbit (or horse or goat) antiserum. The serum proteins (antigens) and the animal antiserum (antibodies) diffuse through the medium; whenever an antibody encounters its homologous antigen, precipitation occurs, forming a band or arc. The position of the bands is determined by the electrophoretic mobility, molecular size and serum concentration of the various proteins. By appropriate selection of antisera and knowledge of mobility characteristics, a large number of proteins can be defined in serum (Figure 2).[45]

On the basis of their immunoelectrophoretic behavior, the gamma globulins have been divided into three major groups: γ_2, γ_{1A} and γ_{1M}. Although these three groups differ antigenically, the differences cannot be attributed to molecular size. For example, some γ_{1A} molecules are the same size as the γ_2 molecules (Table 1).

Carbohydrate content. The γ_{1A}- and γ_1-macroglobulins contain relatively high amounts (10 per cent) of hexose, hexosamine, fucose, and sialic acid, compared with the γ_2-globulins, which contain only 2 to 3 per cent.[31,38] The difference in carbohydrate content appears to be the major factor responsible for the differences in the electrophoretic mobility of the gamma globulins.

Metabolism. Recent studies[1] indicate that in man about 80 per cent of the body content of γ_1-macroglobulins is intravascular, in contrast to about 40 per cent of the γ_2-globulins. The survival time of the γ_{1M}-globulins is short compared with that of the γ_2-globulins (about five days against 23 days), and their rate of synthesis is only 15 to 20 per cent that of the γ_2-globulins. Little is known as yet of the mechanisms that control the synthesis of the various classes of gamma globulin.

Molecular structure. Despite the characteristic difference between the γ_2-, γ_{1A}- and γ_{1M}-globulins, the structure of the components forming their molecules appears to be the same. Recent work[19] indicates that the basic structural component consists of two heavy (H) polypeptide chains, each having a molecular weight of about 55,000, and two light (L) chains, with a molecular weight of about 20,000 each. Disulfide bonds link the four chains, forming a unit. The γ_2-globulin molecules consist of only one such unit. The molecules of the γ_1-macroglobulins are composed of five or six such units (monomers), which are linked together by disulfide bonds. The monomers can be easily split apart by reduction of the macroglobulin molecule at neutral pH with reagents that break the disulfide bonds[12]; this procedure is reversible. The H and L chains can then be dissociated by appropriate methods[19] and separated and recovered by chromatography in urea or strong acids.

Antigenic determinants. A number of recent investigations have been concerned with the properties of the separated H and L chains. Several such studies have shown that the chains of each of the immunoglobulins carry specific antigenic determinants, some of which are common to all three classes and others which are unique to each class.[9,22] More recent work has indicated that the H chains bear the antigenic determinants unique to the intact protein of the γ_2-, γ_{1A}- or γ_{1M}-globulins and the L chains the determinants common to all three groups.[39] Peptide maps have confirmed that the immunologic differences between the L and H chains are on a structural basis. The peptide maps of the L chains of all three immunoglobulins are identical, whereas the maps of the H chains of each immunoglobulin are completely dissimilar.[5,20] Current data also suggest that the H chains of each of the three gamma globulins differ biochemically, in contrast to the L chains of all three, which are closely similar.[20]

The L chains of the γ_2-, γ_{1A}- and γ_{1M}-globulins contain an additional antigenic determinant that permits separation of these proteins into two large classes designated I and II.[28] In normal serum, approximately 60 per cent of the γ_2-molecules have type I L chains and 30 per cent have type II L chains; in the remaining 10 per cent the L chains apparently contain neither type I nor type II determinants.[16,35] In γ_2- or γ_{1A}-myeloma or Waldenström's macroglobulinemia, however, the abnormal protein molecule contains either type I or type II determinants, but never both, and thus is immunologically distinguishable from its normal counterpart.[17,34]

In the case of the γ_2-globulins, the H chains also possess certain antigenic sites that permit further division of these proteins into subgroups γ_{2A}, γ_{2B} and γ_{2C}. These subgroups can be detected by the use of monkey antisera.[13] The normal γ_2-globulin population is made up of all three types of molecules. In γ_2-myeloma, in contrast, only one type of molecule, which may be γ_{2A}, γ_{2B} or γ_{2C}, is present.

Genetic determinants. The L chains of all three immunoglobulins carry the genetically determined Inv serologic factors.[24] The H chains of the γ_2-globulins carry the genetically determined hereditary Gm factors.[22] These two sets of hereditary factors are analogous to hereditary antigens within the red cell (for example, the Rh and ABO antigens). As yet no genetic factors have been localized to the H chains of the macroglobulins. Individual γ_1-macroglobulins, however, have been shown to differ serologically,[11] and the presence of genetic factors restricted to the H chains of the γ_{1M}-globulins appears almost certain.[24]

Antibody activity. Most of the common antibodies have been demonstrated in the γ_2-globulins. Although the γ_{1A}-globulins apparently have antibody activity,[50] their exact function has not yet been established. The γ_1-macroglobulins contain many well-defined antibodies, including anti-A and anti-B isohemagglutinins, heterophile antibody, Rh saline agglutinins, cold agglutinins, most rheumatoid factors, some lupus factors, some Wassermann antibodies, typhoid O agglutinins, antithyroglobulin and most antibodies against gram-negative organisms.[30] Lack of γ_{1M}-antibodies probably explains the increased incidence of infections from gram-negative organisms in the newborn.

Characteristically, macroglobulin antibodies are the first to appear in response to an antigenic stimulus.[2] After injection of typhoid antigen, for example, macroglobulin antibody titers rise promptly and rapidly, reaching peak levels within seven to 10 days of the injection, then decrease with equal rapidity. Detectable γ_2-antibodies appear in the serum later and persist for longer periods. Whether an antigenic stimulus will result in the formation of γ_2- or γ_{1M}-antibodies, or both, apparently depends on a number of variables, such as type of antigen, route of administration, number and frequency of injections and period of immunization.[47] In hemolytic anemia associated with high titers of cold agglutinins, a direct relationship has been demonstrated between the presence of antibodies and clinical symptoms.[25] In diseases such as thyroiditis, rheumatoid arthritis, lupus erythematosus and others, the question of whether the antibodies represent cause or effect remains open.

Antibodies in the newborn. The human fetus receives most of its antibodies by way of the placenta,[53] although a small proportion of the total of antibody molecules is synthesized endogenously. Only the γ_2-globulins are able to pass the placenta. Since neither the γ_{1A}- nor γ_{1M}-antibodies cross the barrier, placental passage of γ_2-antibodies must be related in some way to the H chains unique to the γ_2-globulins. Size alone cannot account for the difference, since most γ_{1A}-globulin molecules, like the γ_2-molecules, are 7S.

This differentiation is clinically important in cases of fetal-maternal Rh incompatibility. The Rh saline agglutinins are macroglobulins and do not pass the placenta. Therefore no fetal damage occurs unless the maternal blood also contains 7S Rh antibodies. Similarly, hemolytic disease of the newborn due to ABO incompatibility occurs only when the mother's blood contains 7S isoagglutinins as is true of normal women with group O blood.[26,27] The serum of women of blood groups A and B normally contains only 19S isoagglutinins; however, if such women are deliberately immunized, they will also form 7S isohemagglutinins.

Hypergammaglobulinemic States

Increased serum concentrations of one, two or all three of the immunoglobulins are found in a variety of disease states. Pronounced increases in only one of the three are found in multiple myeloma and Waldenström's macroglobulinemia. In multiple myeloma, the abnormal protein may be γ_2 or γ_{1A} in type, whereas the macroglobulinemia of Waldenström is characterized by increased levels of γ_{1M}-components. High serum concentrations of γ_{1M}-proteins are also found occasionally in patients with trypanosomiasis,[7,36] and in rare cases in diseases associated with 19S antibodies. In rheumatoid arthritis and lupoid hepatitis, for example, the increase in rheumatoid factors[29] or complement-fixing antibodies to liver tissue,[32] respectively, may be so great (serum titers of 100,000 or more) that these components constitute more than 10 per cent of the total serum proteins. The same is true of the agglutinins in some cases of cold-agglutinin hemolytic anemia.[25] Secondary increases in 7S components may also occur in carcinoma and lymphoma, as well as in a group of disorders of unknown cause that have been termed "monoclonal gammopathies."[55] In a recent series of 400 cases of hyperglobulinemia,[40] about 25 per cent were considered to be in this category.

Abnormal serum immunoglobulins. The paraproteins found in disease differ from their normal heterogeneous immunoglobulin counterparts, in that they are homogeneous, as judged by their known electrophoretic[37] and immunologic[17,34] properties. For example, they contain only one of the two L chain antigenic determinants, in contrast to the normal gamma globulin "population" which includes both type I and type II molecules. Also a γ_2-paraprotein, for instance, never contains more than one of the major Gm factors or more than one of the major Inv factors, whereas normal γ_2-proteins consist of a mixture of molecules, usually with several Gm determinants. The same holds true of the Inv determinants of all three types of gamma paraproteins.

Bence Jones proteins. The urine of many but not all patients with multiple myeloma, and occasionally the serum,[49] contains components of low molecular weight and unique thermal properties called Bence Jones proteins. Chemical and immunologic studies have shown that these proteins are usually dimers of L chains. Like the L chains of the paraproteins, a Bence Jones protein contains either type I or II antigenic determinants, but not both, and no more than one of the Inv factors. Free L chains bearing both type I and II antigenic determinants[16] are present in normal human serum and urine.[4] In several instances the L chains produced by chemical degradation of a myeloma protein proved to be identical with Bence Jones protein from the same patient.[15] It now appears that Bence Jones proteins result from a defect in the mechanism for protein synthesis: either overproduction of L chains or failure to "couple" the chains to form a complete molecule. Presumably the same holds true for what has been called "H chain" disease. Franklin and associates first reported the finding of a gamma globulin of low molecular weight but lacking the thermal properties of Bence Jones protein in the serum and urine of a patient.[23] These proteins resembled free H chains. Subsequently, the finding of similar micro-γ-globulins was reported in an additional four cases.[41]

Waldenström's Macroglobulinemia

In 1944, Waldenström first described "essential" macroglobulinemia, a condition in which the γ_1-macroglobulins make up more than 10 per cent of the total serum proteins.[54]

Etiology. The cause of the disease is unknown. According to one theory, it may result from a malignant change in a cell clone, with resultant overproduction of proteins of one molecular species.[6,33] An alternate hypothesis is that the increase in macroglobulins represents a hyperimmune response to an as yet unidentified antigenic stimulus.[29] Previously, the antigenic homogeneity of the proteins of multiple myeloma and of Waldenström's disease, in contrast to the heterogeneity of normal gamma globulins, was cited as evidence of the malignant nature of these diseases. However, current evidence that the serum of some patients with cold-agglutinin hemolytic anemia contains 19S antibodies in sufficient concentration to meet the criteria for macroglobulinemia[25] tends to support the hypothesis of a hyperimmune response. Furthermore, in antigenic studies of antibodies isolated from individual subjects,[21] all of five 19S gamma globulin cold agglutinins tested proved to be comparable to the paraproteins of myeloma and Waldenström's macroglobulinemia, in that they were homogeneous in antigenic structure (that is, contained only type I antigenic determinants), whereas only one of four rheumatoid factor 19S gamma globulins tested was similarly homogeneous.

Clinical and laboratory manifestations. Waldenström's macroglobulinemia occurs chiefly but not exclusively in men and usually after the age of 50 years. The initial symptoms, such as fatigue, weakness, malaise and visual or auditory disturbances, are vague and nonspecific. Infections, epistaxis and gastrointestinal bleeding are frequent complaints. A few of these patients have persistently low serum levels of 7S γ_2-globulin, and as a result tend to have repeated bacterial infections.

On physical examination, the patient may have purpura, dilated retinal veins ("sausage" veins), retinal hemorrhages and exudates, mild generalized swelling of the lymph nodes and enlargement of the liver or spleen, or both. In some cases, neurologic symptoms indicate involvement of the central and peripheral nervous systems. The delayed hypersensitivity component of immune resistance (in other words, cellular immunity as opposed to the ability to form serum antibody) remains intact.[42]

Anemia, occasionally associated with leukocytosis, and a pronounced increase in the erythrocyte rate are common findings; Bence Jones proteinuria is present in rare cases. Paper electrophoresis of the serum shows a pronounced increase in the gamma globulin peak, usually in the fast gamma zone. The Sia water dilution test for euglobulin is positive in 80 per cent of cases; cryoglobulins (cold precipitable proteins) are demonstrable in some instances, but pyro-γ-globulins (heat coagulable) are rarely present. The serum of patients with macroglobulinemia is extremely viscous, ranging from 5 to 20 viscosity units relative to water (normal, 1.3 to 1.6 units), in contrast to multiple myeloma, where the range is from 1.5 to 4 viscosity units. Because of the increased serum viscosity and hyperproteinemia, cross-matching difficulties and biological false-positive reactions in tests for syphilis may be encountered.

In most patients, the bone marrow is infiltrated with lymphocytoid plasma (L-P) cells, which are rich in carbohydrate; tissue mast cells may also be present.[14] The combination of the two cell types in the bone marrow of a patient is almost diagnostic of macroglobulinemia. Because of their high carbohydrate content, the L-P cells stain positively by the periodic acid Schiff (PAS) reaction; positive PAS stains, however, do not exclude multiple myeloma of the γ_{1A} variety, since γ_{1A}-globulin also contains large amounts of carbohydrate. In macroglobulinemia, L-P cells are also found in the lymph nodes, spleen and liver; in some instances they also infiltrate the perivascular areas of the peripheral nerves and the Virchow-Robin spaces of the central nervous system.

In patients with macroglobulinemia, ineffective erythropoiesis, shortening of the life span of the red blood cells, loss of blood, interference by the macroglobulins with platelet function and other as yet undefined defects contribute to the anemia and bleeding disorders.[8] In studies at the University of California Medical Center, simultaneous determinations of red cell mass by the radiochromium red cell tag method and of plasma volume with radioactive albumin have been carried out on a number of patients with macroglobulinemia and with multiple myeloma. Greatly increased plasma volumes (in the range of 100 ml per kg of body weight) were found in the majority of patients with macroglobulinemia; in contrast, a normal total blood volume in association with a contracted red cell mass was typical of the patients with myeloma.

Renal damage, in the form of para-amyloid disease as seen in multiple myeloma, is rarely found in patients with Waldenström's macroglobulinemia, perhaps because of the low incidence of Bence Jones proteinuria and the intravascular location of the macroglobulins. Osteolytic bone lesions are also seldom seen in macroglobulinemia.

Differential diagnosis. Waldenström's macroglobulinemia must be differentiated from other hypergammaglobulinemic states. Differentiation from multiple myeloma is especially important, since both the prognosis and treatment differ considerably. Obviously, the clinical manifestations are only suggestive, and diagnosis must be based primarily on laboratory findings.

Analytical ultracentrifugation has been widely used to identify the paraproteins, and until recently was considered a dependable means of differentiating Waldenström's macroglobulinemia and multiple myeloma. Reliable sedimentation coefficients are not obtained, however, unless the procedure is carried out properly. The macroglobulins, unlike the γ_2-globulins, are extremely concentration dependent. Their rate of sedimentation depends on the total protein concentration of the solution; the less concentrated the solution, the faster they sediment. For this reason, it is necessary to determine the sedimentation rates at various protein concentrations. These values must then be extrapolated to obtain the sedimentation coefficient at zero protein concentration and 20° C.[43] Since the paraproteins of γ_{1A}-myeloma not infrequently have sedimentation rates ranging from from 13 to 15S, failure to make these corrections could lead to an erroneous diagnosis of Waldenström's macroglobulinemia in a patient with γ_{1A}-myeloma. Failure to consider concentration dependence also accounts in part for the wide variation in sedimentation coefficients reported in early studies of the proteins of Waldenström's macroglobulinemia.[44]

Unfortunately, even when corrected sedimentation coefficients are obtained, analytical ultracentrifugation alone cannot be depended on for diagnosis. Recent observations indicate that two types of pathologic macroglobulins exist, one having a corrected sedimentation coefficient of 17S and the other a corrected sedimentation coefficient of 18.3S.[18] Another study has shown that in γ_{1A}-myeloma, the paraprotein may be of a single type with an S rate of 17 Svedberg units.[52] In patients with this type of γ_{1A}-myeloma, ultracentrifugal analysis would be of little value in indicating the correct diagnosis.

In all cases, the definitive laboratory procedure for diagnosis consists of immunologic studies with specific antisera to γ_2-, γ_{1A}- and γ_{1M}-globulins.

Therapy. Many of the symptoms of macroglobulinemia are attributable to the increased viscosity of the plasma and can be relieved by correction of this condition. If the frequent hemorrhagic episodes are prevented, the life span of the patients is not greatly shortened; the visual defects and poor resistance to infection can be reversed by appropriate treatment. Plasmapheresis[46] has been used successfully to reduce plasma viscosity; in fact, the episodes of epistaxis and gastrointestinal bleeding characteristic of this disease can be regarded as "auto-plasmapheresis." Plasmapheresis has been greatly facilitated by use of a "double-double bag" (Fenwal Laboratories, Morton Grove, Illinois) specifically designed for this procedure. This equipment permits withdrawal of two units of blood, as well as return of autologous red cells, during a 90-minute period, with only one venipuncture. Administration of chlorambucil (Leukeran®), a derivative of nitrogen mustard, which presumably inhibits mitosis of the cells that produce the abnormal proteins, has had beneficial results in some cases.[3]

Splenectomy has been performed on occasion in an attempt to reduce the macroglobulin content of the serum, but is generally considered ineffective.[57] In one case studied by us, however, removal of the spleen for the treatment of concomitant hemolytic anemia was remarkably effective in producing a remission of macroglobulinemia. Macroglobulins completely disappeared from the patient's serum after splenectomy, but began to reappear one year later.

In summary, macroglobulinemia then is a disease state manifested by a striking increase in the serum γ_1-macroglobulins, one of the three types of normal immunoglobulins. Since detailed study of normal γ_1-macroglobulins is hampered by the heterogeneity common to all immunoglobulins, the homogeneous paraproteins of Waldenström's macroglobulinemia are useful models for detailed study of the properties of the γ_1-macroglobulins as a whole.

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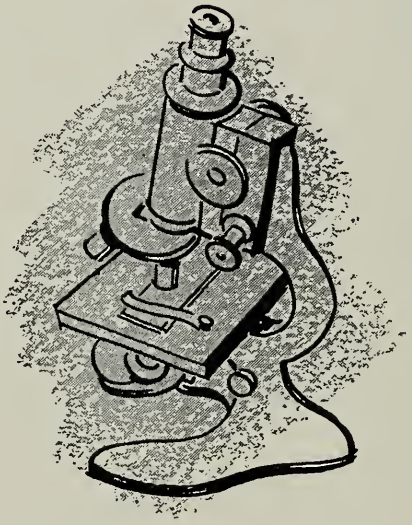

CASE REPORTS

Diagnosis of Acute Abdominal Disease In Paraplegic Patients

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ACUTE ABDOMINAL EMERGENCIES are rarely reported in patients with paraplegia,* despite the fact that there were more than 100,000 paraplegic patients in the United States by 1953,[6] including nearly 6,000 of them in armed services hospitals.[3] The following report is of two paraplegic patients, one of whom had pneumoperitoneum and the other probable pelvic inflammatory disease.

Reports of Cases

CASE 1. An obese 41-year-old paraplegic man was admitted to Franklin Hospital on November 7, 1963, because of a wrist infection and malfunction of a suprapubic cystostomy tube. Complete motor sensory loss below the seventh thoracic root resulted from transverse myelitis after spinal anesthesia in 1946. The suprapubic cystostomy tube, inserted in 1960 because of penile and scrotal edema, had a well-fibrosed tract around it and could be replaced easily. Previous history included a duodenal ulcer, appendectomy, frequent urinary tract infections and calculi.

Physical examination showed inflammation at the operative site of a recent ulnar neurolysis but there were no abnormal abdominal findings. The patient had massive penile and scrotal edema, and the suprapubic cystology tube was not draining. The tube was removed and a catheter was inserted with a stylet. Drainage then was good. Two hours later the patient began to have chills and the temperature rose to 100°F. He vomited bile-colored material and complained of pain in the right shoulder. Antacids gave no relief. The only significant abdominal finding was absence of liver dullness. The hematocrit was 40 per cent and the leukocyte count was 15,400 per cu mm with a leftward shift of the differential. Urinalysis showed moderate proteinuria and a sediment of 400 leukocytes and 200 erythrocytes per high power field. The blood urea nitrogen was 32 mg per 100 ml. Vomited material was positive for occult blood. Roentgenologic studies showed pneumoperitoneum and dilated, fluid-filled loops of small bowel. The presumptive diagnosis was perforated duodenal ulcer.

Exploratory laparotomy showed that the cystostomy tube had perforated its sinus tract. Thick, cloudy uriniferous fluid was present within the peritoneal cavity, and the urinary bladder was extremely contracted. The sinus perforation was closed and a catheter was inserted into the bladder under direct vision. The postoperative course was complicated by hypotension, ileus, peritonitis and signs of acute renal tubular failure. The patient eventually responded to supportive care and antibiotics and was discharged from the hospital 21 days after operation.

CASE 2. An 18-year-old paraplegic woman was admitted to Franklin Hospital for surgical man-

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*Reference Nos. 2, 8, 10, 13 to 15, 16, 21.

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agement of decubitus ulcers. She had become paraplegic after a bullet had lodged in her spinal cord at the level of the 12th thoracic root. Previous history included laminectomy, appendectomy and ureteroileostomy. After admission to the hospital she had acute onset of cramps, abdominal pain, nausea and vomiting. The pain was at first diffuse but later localized to the left lower quadrant of the abdomen. The blood pressure was 140/90 mm of mercury, the pulse rate 120 and the temperature 103°F. Guarding and tenderness were noted in the left lower quadrant of the abdomen but there was no rebound tenderness. Pelvic examination showed a milky vaginal exudate, and pronounced tenderness was noted during cervical manipulation. A tender small mass was felt in the left adnexal area. Motor and sensory function were absent below the level of the 12th thoracic root.

The hematocrit was 39 per cent and the leukocyte count was 14,050 per cu mm with a leftward differential shift. Urinalysis showed five white cells per high power field and a 2-plus reaction for protein. Abdominal roentgenograms showed a patchy gas pattern in the small bowel and poor visualization of renal and psoas shadows. An intravenous pyelogram and retrograde pyelographic examination showed normal kidneys and a functioning ureteroileostomy. A large adnexal mass was found during pelvic examination at the time of cystostomy.

The patient was treated with nasogastric suction, intravenous fluids and antibiotics and became afebrile with symptomatic improvement by the fourth day. She remained afebrile although continuing to have mild lower abdominal pain. On the 13th day severe pain with rebound tenderness in the left lower quadrant of the abdomen developed, but without fever. A barium enema showed no intrinsic bowel disease. Surgical intervention was strongly considered but was withheld in favor of conservative therapy since recurrent salpingitis seemed the most likely diagnosis. She became asymptomatic after supportive therapy and the consensus of the staff was that she had had acute pelvic inflammatory disease.

Discussion

Pneumoperitoneum with peritonitis caused by a suprapubic cystostomy tube has not to our knowledge been previously reported.[14,28,20] Spensley and his coworkers[20] did not mention such a case in their review of unusual causes of pneumoperitoneum and acute abdomen, nor could we find a similar case since Popper[18] first utilized pneumoperitoneum as a sign of perforation of the gastrointestinal tract.

Acute abdominal disease is rarely mentioned in the mortality and morbidity figures of large series of paraplegic patients. The mortality rate from all causes was 15 per cent in 134 paraplegic patients who were observed over a five-year period.[13] The cause of death in 21 of these patients included renal failure (eight patients), coronary occlusion (two patients), cerebrovascular accident (two patients), death from violence (four patients), pulmonary embolus (two patients), pneumonia (one patient) and infectious hepatitis (one patient). The cause of death was unknown in seven patients. Monro[16] analyzed 212 cases of paraplegia but mentioned no cases of acute abdominal emergency. The major complications in that series included sacral decubiti, incontinence, calculi, infections, skeletal muscle spasms and contractures. Botterell[2] reported seven deaths in 103 paraplegic patients. The causes of death included genitourinary sepsis (two patients), intraperitoneal rupture of a perinephric abscess (one patient), uremia (one patient), acute necrosis of the liver (one patient) and coronary thrombosis (one patient). The remaining death was due to an automobile accident.

In contrast to these clinical studies it is important to note the report of Dietrick and coworkers,[6] who studied 55 paraplegic patients at autopsy. They found that six patients (11 per cent) had acute abdominal catastrophes. These included three patients with ruptured bladders, one with intestinal obstruction and a ruptured cecum, one with a small bowel volvulus and ileal gangrene and one with overwhelming peritonitis from acute phlegmonous cystitis.

The largest group of paraplegic patients are inpatients of the Veterans Administration Hospital system. There were 2,048 such patients as of March 1964.[12] Although the specific incidence of acute abdominal disease in these patients is unknown, it is not believed to differ from that of the nonparaplegic population.[12] The Spinal Cord Injury Service of the Long Beach Veterans Hospital has had 24 patients with acute abdominal emergencies in the last 18 years, and a correct preoperative diagnosis was made in 18 of these patients.[1] Twelve of the patients had appendicitis and the other 12 had perforation of a viscus—of the colon in six cases, of a duodenal ulcer in three, of a tuberculous appendix in one, of the gallbladder in one and of an inflamed ileum in one.

Depending upon the level of neurologic impairment, the diagnosis of the "acute abdomen" in a paraplegic patient may be extremely difficult or it may be relatively apparent. Cervical or high thoracic-cord lesions preclude pain perception through the usual nerve pathways and also destroy or distort important diagnostic reflexes. However, low thoracic cord or cauda equina lesions do not prevent the appearance of most of the usual signs and symptoms. Table 1 lists the causes and clinical findings in paraplegic patients with acute abdominal conditions reported during the last 18 years. In spite of varying sites of spinal cord lesions in these patients, all had some manifestations of abdominal distress. The most prominent symptom was pain, often of a visceral nature, which was usually sufficient to lead to investigation and treatment of the abdominal lesion. The physical findings were rarely diagnostic and consisted mainly of deep diffuse tenderness without localizing signs.

The site of the neurologic lesion determined the signs and symptoms in most cases. Patients with cervical or upper thoracic cord lesions reported by Hoen and Cooper[10] complained of pain which was "dull, oppressive, and diffuse." Patients with lesions of the lower thoracic cord described by Greenfield[8] had the same pain pattern usually associated with acute abdominal disease. One of the patients herein reported upon (Case 1) had a lesion of the upper thoracic cord but did not have localizing signs or symptoms of abdominal distress. The second patient, who had a lesion of the lower thoracic cord, had all the findings expected in any person with acute intra-abdominal disease.

Deep visceral pain is associated with disturbances of an intra-abdominal viscus (distention or spasm) and is thought by some investigators to be transmitted by afferent fibers via sympathetic nerves.[21] Innervation of intra-abdominal viscera is shown in Table 2. However, this and similar outlines must be regarded as generalizations of the relationship between the level of neurologic involvement and symptoms and signs, since several well documented exceptions have been reported.[7,8,10,22]

One might question whether the paraplegic patient, because of the disruption of gastrointestinal-tract innervation, is more prone to develop acute intra-abdominal disease than are normal persons, but there seems to be no definite evidence for this. Keeler and Rusk[11] studied the gastrointestinal activity of paraplegic patients with serial x-ray films and found no correlation between gastrointestinal function and the neurologic disease. They found that except for the anal sphincter the bowel functioned independently of the neurologic disease. Robertson and Guttman[19] studied the process of labor in paraplegic women and found that all of them had normal polarized uterine contractions irrespective of the location of the neurologic lesion. However, in paraplegic women with lesions at or above the fifth thoracic vertebrae dilatation of the uterine cervix tended to produce a visceral autonomic stress syndrome, characterized by vasoconstriction, increased blood pressure, lowered pulse and pulse pressure and decreased skin temperature below the site of the lesion. This stress syndrome, termed a "mass reflex," has been reported in patients with spinal cord lesions who have undergone anesthesia and operative manipulation of the viscera or peritoneum.[4,5,9,17] The syndrome has been thought to be due to the imbalance of suprasegmental excitatory and inhibitory reflexes which result from certain cord lesions and cause the cord distal to the lesion to be highly excitable.[4]

The management of the paraplegic patient with an acute abdominal condition hinges upon reaching a diagnosis. Signs and symptoms may be atypical.[8,10] Abdominal pain may be non-existent or dull, diffuse and non-localizing. Nausea and vomiting as well as slight increases in temperature are frequent occurrences in paraplegic patients and are not diagnostic. Temperatures above 103°F suggest a urinary tract infection rather than an acute abdominal emergency. Physical findings are masked. Abdominal tenderness, guarding and rigidity are usually absent. Bowel sounds are rarely significant unless they change in character.

While not confined to cases of acute abdominal disease, the appearance of headaches, changes in blood pressure, sensations of local flushing or heat, and increased reflex irritability are of great value as harbingers of intra-abdominal distress. In this connection it is important to emphasize that the patient with long-standing paraplegia is usually able to recognize when he is ill even though he cannot be specific about his symptoms.

Laboratory studies are often not diagnostic.

TABLE 1.—*Summary of Reported Cases of Acute Abdominal Disease in Paraplegic Patients (1945-1964)*

Author	*Location of Neurological Lesion*	*Symptoms and Signs*	*Diagnosis*
Hoen and Cooper[10]	C-6	Epigastric pain; no abdominal tenderness	Gastric ulcer seen on gastrointestinal series
	C-8	Nausea, vomiting; dull, diffuse abdominal pain; pain at the right costovertebral angle	Renal and ureteral calculi
	T-7	Dull, diffuse abdominal pain	Bowel obstruction
	T-8	Suprapubic pain and tenderness	Bladder perforation
	T-8	Pain in right upper quadrant	Staghorn calculus in right kidney
	C-7	Abdominal distention, hyperperistalsis	Fecal impaction
Greenfield[8]	T-12	Pain and tenderness, right lower quadrant	Chronic inflammation of appendix
	T-9	Pain and tenderness, right lower quadrant	Chronic inflammation of appendix
	T-1	No abdominal findings; chills and fever (100°F.)	Chronic cholecystitis and cholelithiasis
	T-3	Pain in right upper quadrant, radiation to tip of scapula	Chronic cholecystitis and cholelithiasis
	T-11	Pain in left lower quadrant and fever (101°F.)	Perisigmoid abscess
	T-10	Auto accident; no abdominal pain; hypotensive; tympanitic upper abdomen	Ruptured spleen followed by postoperative subdiaphragmatic abscess
Botterell et al.[2]		No clinical summary	Intraperitoneal rupture of perinephric abscess
Watkins[21]	L-1	Subcostal pain in left upper quadrant, shock, dyspnea	Diaphragmatic herniation of abdominal viscera
Dietrick et al.[6]		No clinical summary	3 ruptured urinary bladders— 1 ruptured cecum 1 ileal gangrene 1 phlegmon of urinary bladder
Bors[1]		No clinical summary	12 appendicitis— 6 perforated colon 3 perforated duodenal ulcer 1 perforated tuberculous appendix 1 ileitis with perforation 1 perforated gallbladder
Wanebo, Webb and Combs	T-8	Nausea, vomiting, fever (100°F.); no abdominal pain or tenderness	Intraperitoneal perforation with peritonitis from cystotomy tube
	T-12	Nausea and vomiting; pain tender mass left lower quadrant	Acute pelvic inflammatory disease, left salpingitis

Legend: C=Cervical; T=Thoracic; L=Lumbar.

TABLE 2.—*Segmental Sensory Innervation of the Viscera*

Organ	*Superficial Areas to Which Pain Is Referred*	*Vertebral Level for Entrance of Visceral Afferent Axons Into Spinal Cord*	*Peripheral Visceral Pathway*
Liver and gallbladder	Right upper quadrant and right scapula	Thoracic—6*, 7, 8, 9*	Major splanchnic nerves
Stomach	Epigastrium	Thoracic—6*, 7, 8, 9*	Major splanchnic nerves
Small intestine	Umbilicus	Thoracic—9, 10, 11,	Major splanchnic nerves
Colon—			
Ascending	Suprapubic	Thoracic—11*, 12 lumbar—1	Lumbar chain and preaortic plexus
Sigmoid and rectum	Deep pelvis and anus	Sacral—2, 3, 4	Pelvic nerves
Kidney	Loin and groin	Thoracic—11*, 12 lumbar—1	Renal plexus via least splanchnic nerve and upper lumbar rami
Ureter	Loin and groin	Lumbar—1, 2	Renal plexus and upper lumbar rami
Bladder—			
Fundus	Suprapubic	....	Lower intercostal nerve
Bladder neck	Perineum and penis	Sacral—2, 3, 4	Pelvic nerves
Uterus—			
Fundus	Suprapubic and lower back	Thoracic—11, 12 lumbar—1	Superior hypogastric plexus
Cervix	Perineum	Sacral—2, 3, 4	Pelvic nerves

*Root levels which are in question.

Modified from J. C. White, R. H. Smithwick and F. A. Simeone, The Autonomous Nervous System, Macmillan Co., New York, 1952, pp 126 to 139.

Leukocytosis and pyuria frequently occur in the "normal" paraplegic and are of diagnostic significance only if they become more severe. Radiologic studies are the most helpful aid to diagnosis. The presence of dilated, fluid-filled intestinal loops, pneumoperitoneum or calculi may establish the diagnosis. Of utmost importance are close observation of the paraplegic patient and an intimate knowledge of his particular reaction to certain stresses. Deviation from a patient's own norm of well-being may be the only sign of an acute abdominal emergency.

Operation should be performed soon after the diagnosis is reached or after reasonable diagnostic efforts have been made. Care must be exercised to avoid hypovolemia and profound hypotension, which are particularly dangerous in paraplegic patients.[23]

Summary

Two cases of acute abdominal emergencies in paraplegic patients are reported. One patient, a 41-year-old man, had pneumoperitoneum and the second patient, an 18-year-old woman, probably had pelvic inflammatory disease.

Diagnosis of abdominal disease in paraplegics with high thoracic or cervical cord lesions is particularly difficult because of absence or distortion of classical signs and symptoms of acute intra-abdominal disease. Close observation of the paraplegic, knowledge of his particular reaction pattern to stress, and judicious laboratory studies are necessary to establish diagnosis. When indicated, operation should be performed early after diagnosis, or after reasonable diagnostic efforts have failed.

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Lactic Acidosis and Phenformin Intoxication

Report of Two Cases with Review of Literature

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SINCE Ungar and coworkers[24] drew attention to the hypoglycemic effect of phenformin (N′-β-phenethylbiguanide) in different species of animals, this drug has been widely used in this country. Even so, the mechanism of action is still not clear.[6,20,25,28] Steiner and Williams[20] suggested that hypoglycemia caused by phenformin is achieved through the so-called "Pasteur effect" with acceleration of anaerobic glycolysis and resultant accumulation of lactic acid. Metabolic acidosis in patients on phenformin has been reported, [10,17,25,26,27] which Walker and coworkers[25] and Lexow[17] suggested might be caused by increased lactic acid production. This view has been supported by in vitro studies of Tyberghein and Williams.[23] There is also in vivo evidence that hyperlacticemia with slow elimination of serum lactic acid after exercise occurred in patients taking phenformin[3,8,25]; but Bernier and coworkers[2] and Shepardson and his associates[19] were not able to confirm this.

Lactic acidosis as a clinical entity with definite diagnostic and prognostic criteria was emphasized by the investigations of Huckabee.[11-15] Phenformin as a cause of so-called "irreversible" lactic acidosis (group 2B patients as defined by Huckabee) was documented in six cases.[2,7,21] Although the evidence for phenformin as the etiologic agent was strong, this was not definitely proved inasmuch as all of the patients were in shock with the exception of one case[7] in which acidosis appeared to precede shock. Other investigators, including Danowski, also questioned that phenformin is the primary etiologic agent in "the lactic acidosis syndrome."[4]

Two patients, both diabetic and both receiving phenformin therapy, were recently clinically evaluated at San Joaquin General Hospital, Stockton.

Reports of Cases

CASE 1. A 62-year-old white woman with chronic alcoholism and diabetes of eight years' duration, was admitted on August 30, 1963, to San Joaquin General Hospital for the tenth time because of preexisting hemiparesis, incontinence of urine and feces, and a family care problem.

Her previous admissions dated back to 1951 when she was admitted for chronic alcoholism and bronchitis. She was found to have diabetes mellitus in 1955, and hepatic cirrhosis was confirmed by liver biopsy in 1956. Reasons for admission on other occasions included a Colles fracture, pneumonia, dislocated left shoulder with fractured left humeral head, chronic alcoholism, diabetes mellitus and left hemiparesis with mental deterioration. Her diabetes was mild in nature and it was well controlled with 10 units of NPH insulin daily. An electrocardiogram taken in 1961 was within normal limits.

The patient was obese, had blood pressure of 180/80 mm of mercury, a pulse rate of 96 per minute, a respiratory rate of 20 per minute and body temperature of 100°F. She was disoriented and confused. Other significant physical findings included absence of pedal pulses and left femoral pulse, diminished right femoral and carotid pulses, and generalized weakness. Heart, lung and abdominal examinations were within normal limits.

Admission laboratory work showed a hematocrit of 37 volumes per cent, leukocytes numbering 9,000 per cu mm with a normal differential count, blood urea nitrogen of 18.5 mg, creatinine of 0.6 mg and fasting blood sugar of 99 mg per 100 ml. Urinalysis showed a two plus reaction for albumin and moderate bacteriuria, 10 to 20 red blood cells and 5 to 10 white blood cells per high power field, but no sugar and no acetone. Coliform bacilli were cultured from the urine. An x-ray film of the chest was within normal limits.

Initial impression was (1) old cerebrovascular accident with left hemiparesis, (2) diabetes mellitus with questionable renal lesion, (3) Laennec's

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cirrhosis, (4) generalized arteriosclerosis with chronic brain syndrome.

The therapeutic plan was to attempt to control the diabetes with oral hypoglycemic agents, then to transfer the patient to a nursing home for further care.

The patient's course in the hospital was unremarkable. She was given an 1,800 calorie diabetic diet. Tolbutamide 0.5 gm twice a day was started on September 2, 1963, and increased to 1 gm three times a day by September 14, 1963. Because of poor control of diabetes, chlorpropamide 250 mg twice a day was tried on September 17, 1963, but this also met with failure. Up to this time the fasting blood sugar ranged between 180 and 220 mg per 100 ml. Administration of phenformin timed disintegration tablets, 50 mg twice a day was initiated on September 24, 1963, and tetracycline 250 mg every six hours was started on September 26, 1963, because of continued bacteriuria. On September 29, 1963, the patient vomited twice, complained of slight abdominal pain, and refused to eat. She was thought to have diabetic acidosis, although her pulse, blood pressure and respiration were stable. Blood sugar was 170 mg per 100 ml with a negative reaction for serum acetone. Serum electrolyte studies showed total carbon dioxide of 8.7 mEq, sodium of 142 mEq, chloride of 106 mEq, and potassium of 5.4 mEq per liter. The patient was given 15 units of regular insulin and the next day she was found to be perspiring profusely, her skin was cold and clammy and she was unable to answer questions. The blood pressure was 120/60 mm of mercury, the pulse was 120 per minute and the fasting blood sugar was 179 mg per 100 ml. The urine was negative for acetone. An electrocardiogram showed no evidence of myocardial infarction and no changes compared with one taken a year previously.

On October 1, 1963, phenformin was discontinued and therapy was changed to 20 units of NPH insulin daily. The blood pressure at that time was 130/70 mm of mercury. Total carbon dioxide was 8.3 mEq per liter of serum and the blood sugar was 72 mg per 100 ml. The hypoglycemic symptoms were relieved by intravenous administration of glucose. Next day the blood urea nitrogen was 108 mg and blood sugar 76 mg per 100 ml and the blood pH was 7.2. Serum lactic acid* was reported to be 107 mg per 100 ml (normal 5 to 20 mg). The blood pressure ranged between 60/0 and 70/50 mm of mercury. Diaphoresis continued but the patient would open her eyes when her name was mentioned. Treatment included 5 per cent dextrose in water intravenously (1,000 ml in 8 hours) with 10 units of aqueous insulin and 1 ml Borocca C® (parenteral vitamin B complex with C) per liter of solution, nasal oxygen, 50 mEq of potassium chloride daily, and a total of 500 ml of sodium bicarbonate solution (0.89 mEq per ml strength) intravenously at 20 drops per minute. No attempt was made to treat the hypotension with vasopressor agents. After 12 hours of therapy total serum carbon dioxide was 40 mEq, sodium 135 mEq, chloride 85 mEq, and potassium 3.5 mEq per liter, and blood sugar was 360 mg per 100 ml. Urine was negative for acetone, and blood urea nitrogen was 36 mg per 100 ml. On October 4, 1963, carbon dioxide was 34, sodium 138, chloride 102 and potassium 4.1 mEq per liter. Blood urea nitrogen was 27 mg and fasting blood sugar was 200 mg per 100 ml. Leukocytes numbered 7,000 cu mm with differential count within normal range. The patient was ambulating with help. The electrolytes remained stable thereafter, and the patient's blood sugar was controlled by administration of 15 units of NPH insulin daily. On October 29, serum lactic acid was 11 mg per 100 ml and pyruvic acid was 0.2 mg per 100 ml (normal 0.5 to 1.5 mg). The patient was transferred to a nursing home.

CASE 2. A 69-year-old white woman was admitted November 7, 1963, to San Joaquin General Hospital for the first time with chief complaints of nausea, vomiting and lethargy of five hours' duration. According to the referring physician and to her family, she was known to have had diabetes for five years and hypertension for seven years. For the past year, diabetes was controlled with diet and phenformin, 25 mg three times a day. The patient was also taking Enduronyl® (methychlorthiazide and deserpidine) twice a day for hypertension. Since February 1963, she had noted intermittent episodes of nausea, vomiting and diarrhea. She was found to have pyuria, bacteriuria and azotemia (non-protein nitrogen —125 mg per 100 ml) in March 1963, and an upper gastrointestinal series at that time showed a cicatrized duodenal ulcer and pronounced calcification of the abdominal vessels. Sulfamethoxazole (Gantanol®) was given for the urinary tract infection.

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*Determined by Bioscience Laboratory in Los Angeles using the method of Barker and Summerson.[1]

On physical examination the patient was obese and appeared seriously ill. The temperature was 98°F, the pulse rate was 74 per minute, respirations 22 per minute and the blood pressure 140/80 mm of mercury. (In March 1963 it had been 150/80.) The veins in the neck were flat, the lungs were clear with no evidence of pleural effusion. The liver was not enlarged or tender to palpation and there was no pitting edema of the extremities. The heart was enlarged but no murmurs were heard. The peripheral pulses were palpable bilaterally, and results of a neurological examination were within normal limits.

Urinalysis was within normal limits, with specific gravity of 1.010 and no reaction for sugar or acetone. The hematocrit was 36 volumes per cent. Leukocytes numbered 20,300 per cu mm with the cell differential within normal range. Blood urea nitrogen was 44 mg and blood sugar 206 mg per 100 ml. Reaction for serum acetone was negative. Carbon dioxide was 4.4 mEq, chloride 91 mEq, sodium 138 mEq and potassium 3.9 mEq per liter. An x-ray film of the chest showed no abnormalities. An electrocardiogram was consistent with left ventricular hypertrophy but there was no evidence of acute myocardial infarction.

The admission impression was lactic acidosis secondary to phenformin intoxication, arteriosclerotic heart disease with hypertension and left ventricular hypertrophy, and chronic duodenal ulcer by history. Blood specimens were obtained for determination of serum lactic acid and pyruvic acid (1:6 plasma-trichloroacetic acid filtrate), and the contents were reported to be 210 mg and 0.9 mg per 100 ml, respectively.

The patient was treated with 1,500 ml of 5 per cent dextrose in water and sodium bicarbonate (66.7 mEq) infused over a four-hour period. Electrolyte studies three hours after treatment showed carbon dioxide of 7 mEq, chloride of 69 mEq, sodium of 130 mEq and potassium of 5.3 mEq per liter, sugar of 288 mg per 100 ml. Reaction for serum acetone was negative. The patient went into shock with cardiac arrest despite vigorous treatment and died seven hours after admission.

At autopsy bilateral pulmonary edema was observed. The heart showed left ventricular hypertrophy and pronounced myocardial fibrosis. The liver and kidneys were grossly normal.

Microscopic examination showed myocardial fibrosis, atrophy of pancreatic acini, ectasia of pancreatic ducts, normal pancreatic islet cells, cystic atrophy of the endometrium and a nodular colloid goiter. The kidneys showed arterial nephrosclerosis, focal chronic pyelonephritis and decided cloudy swelling of the epithelium of the distal convoluted tubules.

Comment

Huckabee[14,15,16] observed that hyperlactatemia can be induced by hyperventilation or by infusion of glucose, insulin or epinephrine. The increase in serum lactate in these conditions is associated with a concomitant rise in serum pyruvate, so that the serum lactate to pyruvate ratio of 10:1 is maintained (Group 1). Hyperlactatemia is also observed in conditions associated with severe hypoxemia and circulatory collapse, in which greater than 60 per cent "excess" lactate (XL)* is obtained with an increase in serum pyruvate. These can be reversed by treatment of the basic disorder with oxygen administration or by transfusion (Group 2A) and by administration of methylene blue.[22] There is yet another condition associated with the presence of "excess" lactate in which neither hypoxemia nor circulatory collapse is present, and in which the immediate cause is not apparent (Group 2B). Huckabee proposed that it is due to tissue anorexia and he called it "lactic acidosis." Patients in this group often die, and treatment with alkali is often futile.

The diagnosis of lactic acidosis is made by exclusion of other causes of acidosis and by showing the presence of excess lactate in the serum. A thorough history and physical examination, serum electrolyte studies, determination of arterial blood pH and oxygen saturation, renal function tests and determination of blood acetone are essential aids. When acidosis cannot be accounted for, lactic acidosis should be suspected and serum lactic acid and pyruvic acid levels should be checked.

While lactic acid and blood pH determinations were available in Case 1 and both lactate and pyruvate were measured in Case 2, arterial oxygen saturation could not be measured due to limited laboratory facilities. Since pyruvic acid was not

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$$*XL = (L_1 - L_0) - (P_1 - P_0)\,\frac{L_0}{P_0}$$

L_1=observed lactate

P_1=observed pyruvate

L_0 and P_0=normal values for lactate and pyruvate

Excess lactate is derived from the equation

$$\text{Lactic acid} + \text{DPN} \rightleftarrows \text{DPNH} + \text{pyruvic acid}$$

done initially in Case 1, we cannot determine whether hyperlactatemia was due to the presence of "excess" lactate or not. However, the patient was resting in bed, was not hyperventilating and was not receiving any medicine except for phenformin and tetracycline. She probably did not belong to Group 1 patients described by Huckabee. Clinically, she was not anoxic and her condition did not improve with nasal administration of oxygen. Acidosis preceded shock in this case, and the acidosis alone was treated without specific shock therapy. The fact that shock reversed after correction of the acidosis would suggest that lactic acidosis may be the cause of the circulatory collapse. For this reason, it would be unlikely that this case of lactic acidosis belonged to Group 2A. However, the improvement of the patient is unusual, since only one patient with lactic acidosis reported to date has survived, and in that case hemodialysis was carried out.[7] There have been no reports of survival in this group with alkali therapy alone. Tranquada[21] showed that the blood phenformin level rose (up to 20 mg per ml) when the drug was given to patients with poor renal function. In the cases he reported, the patients died of lactic acidosis. Daweke[6] suggested that a normal therapeutic level of biguanide (4 to 5 mg per ml) would not cause an increase in blood lactic acid, whereas a "high" level would. However, he did not specify what this level was. In Case 1 herein reported, there was laboratory evidence of poor renal function and the patient could possibly have had elevated blood phenformin, resulting in lactic acidosis, even when she was taking therapeutic doses of phenformin.

Based on our experience in Case 1, the diagnosis of lactic acidosis (Group 2B) was more obvious in Case 2 in light of the calculated "excess" lactate. The patient was azotomeic, but this condition was probably not severe enough to cause acidosis of the degree noted. She was not in diabetic acidosis, as judged by a negative reaction for serum acetone and only slight elevation of blood sugar. Acute myocardial infarction can sometimes cause circulatory collapse and lactic acidosis, but the patient did not have electrocardiographic evidence of acute myocardial infarction, and only myocardial fibrosis was found at autopsy.

From our experience with the two cases herein and the reported experience of other investigators,[2,21] we believe that acidosis preceded shock, and that lactic acidosis in these cases were not caused by shock. We were well aware that pulmonary edema can cause anoxia, which may induce lactic acidosis.[14] The clinical course of the patient in Case 2 was followed very closely, and we were satisfied that at no time was there any physical evidence of pulmonary edema. An x-ray film of the chest supported that belief. It is believed that the pulmonary edema noted at autopsy was acute in nature and probably occurred terminally. All the known causes for lactic acidosis as discussed by Huckabee[14-16] seem to be unlikely in this case, and there is reason to suspect phenformin intoxication as the cause of death.

The issue of the causal relationship between phenformin toxicity and "irreversible" lactic acidosis is further confused by a recent report of Daughaday and coworkers.[5] These investigators reported at least two documented cases in which lactic acidosis developed in patients who were not taking phenformin. This would suggest that diabetes alone can lead to lactic acidosis. It is possible, therefore, that in reported cases in which lactic acidosis developed in diabetic patients taking phenformin, the disease and not the drug was the cause. Daughaday[5] and Huckabee[16] both suggested that tissue anoxia may be the cause of lactic acidosis. It is conceivable, therefore, that a drug like phenformin could trigger the formation of lactic acidosis in a diabetic patient who is susceptible to the development of lactic acidosis. One wonders if phenformin could induce lactic acidosis in a non-diabetic person, with or without poor renal function. In order to establish a causal relationship between phenformin and lactic acidosis, many variables such as are encountered in daily clinical practice should be eliminated. Perhaps this may be accomplished in controlled animal experiments.

Danowski[4] and Huckabee[16] pointed out that death can occur even though serum carbon dioxide and blood pH are corrected, for the serum lactate level might still be elevated. This would imply that lactic acidosis causing death might be more than simple acid-base imbalance; that it may be a reflection of severe tissue anoxia of an irreversible nature.

Phenformin does not lower blood sugar in normal humans, but it does in animals.[28] It exerts its hypoglycemic effect only on persons with diabetes. It is said to inhibit oxidative phosphorylation, thus decreasing Kreb's cycle activity, and to inhibit certain oxidative enzymes, namely, succinic dehydrogenase and cytochrome oxidase. The result is tissue anoxia which may lead to increase in glucose uptake by peripheral tissue (Pasteur effect) and increased anaerobic glycolysis, thus explaining the increase in lactic acid production.[28]

The treatment of lactic acidosis has been quite discouraging. Sodium bicarbonate has been tried unsuccessfully. Moore and Bernhard[18] reported successful treatment of hyperlactatemia produced by cardiopulmonary by-pass with a new, non-ionic, buffering agent which can traverse cell membranes readily. This is a promising report and worthy of further investigation. Hemodialysis was used successfully by Ewy in one case.[7] More recently, Tranquada[22] reported reversal of the serum lactate and pyruvate ratio in patients treated with methylene blue intravenously, but the patient died.

Before all the conflicting data on the relationship of phenformin to lactic acidosis is resolved and adequate therapy becomes available, a better clarification of the mode of action of phenformin as well as the further reporting of clinical experience with this condition will be necessary.

Summary

Two cases of lactic acidosis associated with phenformin administration in diabetic patients are reported. Both patients were treated with intravenous infusions of alkali. One recovered.

The diagnosis of lactic acidosis was suspected when all common causes for metabolic acidosis were absent. This was confirmed with the demonstration of the presence of serum excess lactate (XL) and a relatively normal or slightly increased serum pyruvate.

The causal relationship between phenformin administration and lactic acidosis was questioned, since lactic acidosis had been reported to occur in diabetic persons who were not taking this drug.

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Cuffed Tracheal Tube

A Report of Two Complications

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THE GROWING ACCEPTANCE of tracheostomy and the broadening indications for it have engendered reports of a growing list of technical and pathological morbidities associated with the procedure.[4-6,8,9] The cuffed tracheal tube, whether used with tracheostomy or with orotracheal intubation, has potential dangers which have been documented.[5,7] This presentation cites two cases in which a tracheal cuff was inadvertently hyperinflated, with fatal result in one.

CASE 1. A 71-year-old man with esophageal cancer underwent esophago-colo-gastrostomy with ileostomy and pyloroplasty. Postoperative pneumonia and psychotic reaction developed, and intermittent orotracheal intubation with positive-pressure ventilation was used during therapy. Shortly after one of the periodic ventilation treatments was begun the patient became dyspneic. An attempt to pass a suction catheter through the orotracheal tube to see if mucous plugs were blocking the airway was unsuccessful. To release the pressure of the tracheal cuff the clamp was removed from the inflating tube, and the pilot balloon promptly deflated. Still the suction catheter could not be passed. Despite the deflated pilot balloon, hyperinflation of the cuff was suspected and the inflating tube was cut near the patient's mouth. There was an immediate outpouring of air, but the patient soon died.

CASE 2. A 43-year-old man had a traumatic cerebral and pulmonary contusion with fractures of the clavicle and eight ribs. Tracheostomy helped alleviate subsequent atelectasis, pneumonia and depressed swallowing reflex. On one occasion as the tracheal tube was being inflated in preparation for a positive pressure breathing treatment, the inflating syringe seemed to be working against excessive resistance. Although the pilot balloon was deflated, the patient coughed as if having tracheal irritation. Examination showed that no air was going around or through the tube as would have been expected had the cuff been deflated. The tracheostomy tube was replaced. Nothing abnormal could be found with the cuffed tube, the pilot balloon or the inflating tube.

Comment

In the first case there were technical errors caused by (1) sticky rubber in the inflating tube of an orotracheal cuffed tube that had been previously used but was thought to be functioning adequately and (2) clamping the inflating tube between the pilot balloon and the air cuff (rather than between the balloon and the opening to the inflating tube). When the inflating tube lost its patency due to repeated clamping over a sticky region, a one-way valve effect was created. Several treatments by an otherwise safe amount of inflating proved additive to the cuff, with eventual obstruction of the airway.

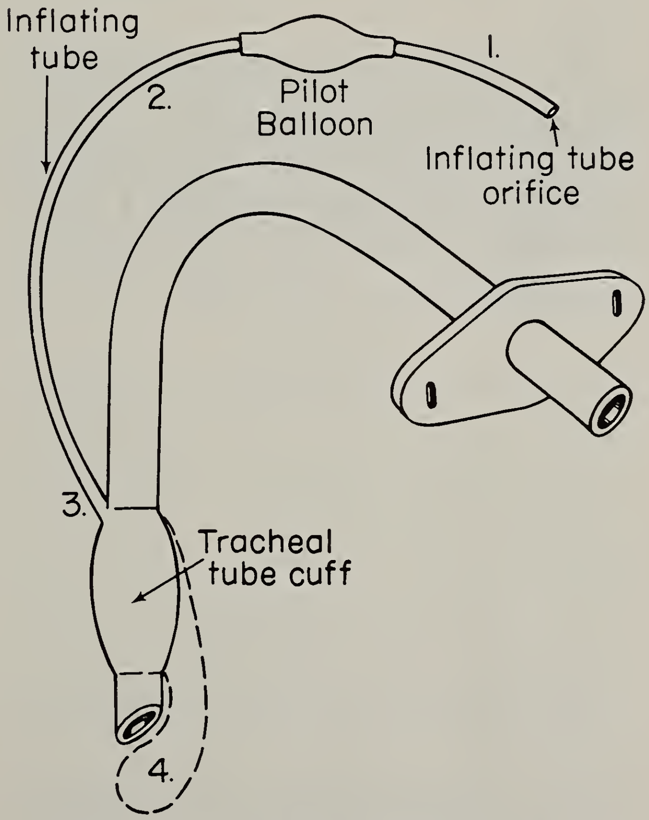

Figure 1.—Pressure-cuff on tracheostomy tube (or on endotracheal tube). 1. Preferred site for applying clamp to maintain air pressure inside cuff. 2. Danger-site for clamp application. 3. Danger-point (for kinking) at air-cuff inflating tube junction. 4. Schematic illustration of hyperinflated cuff.

From the Veterans Administration Hospital, Long Beach.
Submitted March 10, 1965.

The second case illustrates a complication of which other observers[9] have warned. In this case, a simple kink in the tube most likely was at fault. As in the preceding case, air could be inserted into the cuff under greater-than-usual pressure, and again the pilot balloon proved misleading.

Ultimately the fault in each case lay in defects of the inflating tube. Preventing these complications can be achieved by one or more of the following measures: (1) Placing the clamp which secures cuff-pressure over the inflating tube between the pilot balloon and the orifice of the inflating tube; (2) Using an air-tight check (usually via a "disposable" plastic syringe) on the exact amount of air inserted into, and then removed from, the cuff; or (3) Using no clamp and leaving an air-tight syringe attached to the inflating tube, the proper pressure being maintained by taping the plunger to the barrel at the appropriate level; or (4) Using the technique recommended by Martinez[7] in which the same intermittent air pressure which ventilates the patient intermittently inflates the tracheal tube. The latter technique is under development.

Summary

Two cases—one fatal—of complications in the use of tracheal cuffs are presented. In both cases the difficulty was due to hyperinflation of the cuff (one an orotracheal cuff, the other a standard tracheostomy cuff) due to malfunction of the inflating tube. Corrective and preventive measures are mentioned.

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Ethanol-Induced Hypoglycemia

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CASES OF HYPOGLYCEMIA occurring after ethanol ingestion have been reported frequently in recent years. As experience has accumulated, it has been found that a period of fasting occurs before the hypoglycemic reaction. In many of the reports the patient was first seen in coma of unknown cause.

Most current reviews of coma neglect this entity; and the frequent association of alcoholism with epileptic seizures, hepatic failure, cerebrovascular accidents, head trauma, hypertensive encephalopathic states and delirium tremens tends to obscure the possibility of ethanol-induced hypoglycemic coma. The following case is being presented to stress again the association of hypoglycemia and previous heavy drinking.

Report of a Case

A 42-year-old Negro man had been arrested for intoxication and booked at the city jail several hours before his admission to hospital. While in jail he reportedly had a seizure, injured his head and was brought semi-comatose to the emergency room. He had a history of 20 years of alcoholism with recent excessive intake of tokay wine. He had had previous admissions, for head trauma and for pneumonia. There was no history of seizures.

On physical examination he responded only to painful stimuli by moving all extremities, all equally well. Rectal temperature was 99°F. Except for a slightly wasted appearance, a small abrasion at the left occiput, occasional symmetrically tonic movements of the limbs, bilateral Babinski reflexes and hyperactive deep tendon reflexes, the results of examination were within normal limits.

After an initial specimen of blood was drawn for determination of sugar content (which was later reported to be 17 mg per 100 ml), 50 ml of 50 per cent glucose solution was administered intravenously. Over the subsequent five minutes

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Submitted February 15, 1965

the patient became alert and oriented and neurologically normal.

X-ray films of the skull, abdomen and chest were normal. An upper gastrointestinal tract series showed a deformed duodenal bulb. An electrocardiogram revealed normal sinus rhythm, high voltage with SV_1 plus RV_5 of 37 mm, QS waves in leads II, III and a VF, inverted T waves in leads I and a VL and depressed T waves in leads V_{5-6}. The hematocrit was 40 per cent. Leukocytes numbered 6,700 per cu mm with 58 per cent neutrophils, 38 per cent lymphocytes, 3 per cent eosinophils and 1 per cent basophiles. Urea nitrogen was 13 mg per 100 ml. The icteric index was 6 units; bromosulfalein retention was 4 per cent at 45 minutes; prothrombin concentration was 100 per cent; thymol turbidity was 3.5 units; cephalin flocculation was negative; and total serum protein was 8.60 gm per 100 ml with albumin of 4.34 gm and globulin of 4.26 gm. Urinalysis revealed a trace of protein, absence of sugar and 3 to 4 white blood cells per high power field. Liver biopsy was reported as normal. On lumbar puncture, no abnormalities of the cerebrospinal fluid were noted.

In order to rule out the usual causes of hypoglycemia the following tests were performed: After three days on a 2,800 calorie, 285 gm carbohydrate diet, an oral glucose tolerance test was done with 100 gm of glucose. The result was interpreted as normal.

An intravenous tolbutamide test was next done by infusing intravenously 1 gm of sodium tolbutamide over five minutes. This resulted in a fall of blood sugar from 92 mg per 100 ml to 54 mg at one hour and a return to 69 mg by three hours. This was followed by a 72-hour fast terminated by one hour of vigorous exercise and 2 mg of glucagon injected subcutaneously. This caused a slight fall in blood sugar level with fasting, followed by a rise of 20 mg per 100 ml after glucagon administration and a slow decline after one hour.

In a non-fasting state, the patient ingested 50 ml of 95 per cent ethanol. Blood sugar determinations began with a fasting level of 106 mg per 100 ml and decreased slowly to 86 mg after six hours.

Finally, a fasting ethanol ingestion test was performed by administering 50 ml of 95 per cent ethanol at 61 hours and again at 66 hours of fasting. This test was terminated at 68.5 hours because of a hypoglycemic reaction with blood sugar of 33 mg per 100 ml.

Discussion

Brown and Harvey[2] first associated hypoglycemia with ingestion of denatured alcohols in 1941. They concluded the hypoglycemia was caused by a non-ethanolic ingredient found in these alcohols. However, their attempts to reproduce the hypoglycemia in animals failed.

In 1961, Neame and Joubert[10] described several cases of postalcoholic hypoglycemia associated with mild, transient toxic hepatitis. This hypoglycemia occurred commonly 12 hours after the ingestion of excessive ethanol, but occasionally would not manifest itself for a day or more.

Subsequently there have been several reports of ethanol-induced hypoglycemia and many unproven theories have been advanced as to the biochemical mechanisms involved. Recently Freinkel[7] and Field[5] showed that it is possible to induce hypoglycemia in normal persons as well as in addicts to alcohol merely by preceding the ethanol ingestion with a fasting period. A period of 48 to 72 hours is usually required; however, subjects with marginal hepatic glycogen stores may require only overnight fasts.[6]

Manifestations

The bizarre manifestations of hypoglycemia and common association of alcohol intoxication with the varied causes of coma may obscure the diagnosis. A history of recent poor caloric intake associated with ethanol ingestion would be helpful but is virtually never offered by the patient. Fewer than half of all reported cases have occurred in alcoholics.[5]

Frequently there are no signs of the expected adrenergic reaction to hypoglycemia as is seen during a rapid decrease in blood sugar.[3,8] Instead, only a cerebral reaction occurs, due to a slow decline in blood sugar to profoundly low levels. Because of this, in all reported cases the patients were in semi-coma or deep coma with blood sugar ranging between 12 and 47 mg per 100 ml.[2,8,10] Hypopyrexia—95° to 97°F—has been frequently reported. Findings on neurological examination often are inconsistent. The deep tendon reflexes may be increased or decreased. Vital signs are usually depressed. There may be seizures, generalized tremor and conjugate deviation of the eyes.

Since these varied manifestations tend to obscure the real diagnosis, the possibility of hypoglycemic coma must be raised on the basis of association. It is possible that if the diagnosis is not considered the patient may continue in coma until death or irreparable brain damage occurs.

Differential Diagnosis and Diagnostic Steps

The differential considerations in the diagnosis of hypoglycemia are many and the reader is referred to the standard medical texts. An insulinoma is the most difficult to differentiate, because the intravenous tolbutamide tolerance test when given to an alcoholic after prolonged poor intake of food frequently results in a sustained hypoglycemia simulating the prolonged reaction typically seen with an insulin-secreting tumor of the pancreas.[9] In all other causes of hypoglycemia there is transient hypoglycemia (30 to 40 minutes) followed by a return to normal over an hour and a half to three hours.[4] In the case here reported the blood sugar was normal within three hours.

An insulinoma will usually cause hypoglycemia during a two-day fast. Frequently, however, blood sugar remains normal during this period and decreases only after provocation with vigorous exercise.[3] In the present case the patient fasted for two days and then walked vigorously for an hour without effect. This exercise period was followed by a subcutaneous injection of 2 mg glucagon and the response was subnormal, showing that there was a decrease in hepatic glycogen stores. The hypoglycemia induced by ethanol is always refractory to glucagon.[1]

A standard oral glucose tolerance test after three days of carbohydrate loading is adequate to rule out diabetes mellitus and the functional causes of hypoglycemia. With hepatic disease, this test usually reveals a plateau in the glucose tolerance curve, and other evidence of liver disease is also present. In the case presented, the results of the glucose tolerance test as well as all measurements of hepatic function and a liver biopsy were within normal limits.

If there is evidence of other causes of hypoglycemia such as adenohypophyseal and adrenocortical hypofunction, sarcomata, fibromata and central nervous system disease, these possibilities must be eliminated by appropriate tests.

After all abnormal causes of hypoglycemia have been eliminated, the duplication of the clinical situation by fast and ethanol ingestion may be attempted. After fasting for 68.5 hours and ingesting 100 ml of 95 per cent ethanol, the patient in the present case became confused and diaphoretic, and the blood sugar was 33 mg per 100 ml.

Mechanisms

Past explanations of the mechanism of hypoglycemia have all been inadequate. A simple explanation is lacking. Recent work suggests that ethanol produces hypoglycemia by inhibiting gluconeogenesis and hepatic glycogen synthesis.[1,5] When ethanol is metabolized, it causes changes in co-enzyme systems, resulting in a disturbance of enzymatic control of carbohydrate metabolism. This disturbance causes further glycogen depletion which in turn increases the vulnerability of the liver to the effects of ethanol. This cycle persists until it is broken by the administration of carbohydrate.[7]

Summary

In the case of a 42-year-old Negro man who was in hypoglycemic semi-coma when first seen, the condition was found to be due to ethanol ingestion. Such hypoglycemic reactions are caused by the association of fasting and ethanol ingestion and show varied manifestations. Usually the only suggestion of this state is the association of coma with alcohol and perhaps hypopyrexia. Glucose administration and adequate feeding usually results in complete recovery.

The mechanisms of ethanol induced hypoglycemia remains speculative. Recent studies, however, suggest an ethanol inhibition of gluconeogenesis and hepatic glycogen synthesis.

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California Medicine

EDITORIAL

Dr. Merrill's Departure

Next November 1 when the resignation of Dr. Malcolm H. Merrill as director of the State Department of Public Health becomes effective, California will lose an outstanding public servant and the California Medical Association will lament the departure of a forthright, thoughtful, considerate man with whom for many years the Association has worked closely and comfortably in the promotion of good health and good health care for the people of this state.

Dr. Merrill's administration has been a continuing demonstration of his full realization of the highest purposes of a department of public health. Under his direction, the department's facilities have been exercised with level-headed recognition that the most salubrious climate for the medical well-being of all the people of this state is generated in mutual respect between the department and the physicians in private practice.

The Health Director has been regularly a welcome guest at meetings of the Council of the CMA. Throughout his tenure as director, all negotiations between the Department of Public Health and the CMA have been carried out in an atmosphere of understanding conducive to the best use of all health care facilities, public and private.

The stature of Dr. Merrill's department and the excellence of his performance are not mere provincial marvels known only in public health circles and among private practitioners in California; they are well recognized across the land. He is a past president of the Association of State and Territorial Health Officers and of the American Public Health Association. And last year the consummate honor for workers in the field of public health, the Bronfman Prize for Public Health Achievement, was awarded to him.

Again and again he has been called upon as a consultant to other organizations and for the performance of special missions the world over. Recently he was a member of a mission for the United States Agency for International Development to discuss public health and family planning programs in the host countries, India, Pakistan, the Philippines, Thailand and Turkey.

It was almost inevitable that one with so bright a record of achievement and good will should have many tempting offers of high station elsewhere put before him. Now he has accepted one of them. His resignation was in order that he could accept an appointment with the Federal Government in the Department of State. He will serve in the Medical Research and Development Unit of the Agency for International Development.

Regret his departure though we do, we can take some comfort in the thought that his ability and common-sense will make themselves felt as cogently in his new job as they did in the directorship he soon will quit here.

Pain and Cruelty

PHYSICAL PAIN is a common experience. Each of us knows first hand that it is evil. It is well known that there is more to pain than the mere sensation. We do distinguish the nerve endings where stimulation, mechanical, electrical or chemical, produces the sensation of pain. We also know the tracts in the spinal cord where pain sensations run. But there is a central component that gives pain its intolerable quality. It is not known for sure whether this is a neural activity of the cerebrum or of the basal ganglia. Certainly operative interference with the frontal lobes (leucotomy) can lessen or remove the pain quality from normally painful sensations.

Inference of pain in other persons subject to such injuries as give pain to oneself is universal. Extension of this inference to domestic and wild mammals is nearly universal, and extension to all vertebrates, warm- and cold-blooded, is common. A few people are convinced that all life is sensitive and can suffer pain. One is occasionally admonished: "Never burn flowers." The devout Hindu, cultivating the saintly life, wears a mask over nose and mouth so as to avoid inhaling insects and so injuring or killing them.

The intolerable nature of pain induces a psychological reaction, not only in the person suffering the pain, but in persons only observing (inferring) pain suffered by other persons. The psychological reaction is unpleasant in all degrees according to the observer's sentimental proximity to the object in which the pain is inferred. There is therefore a hierarchy: Self > wife and children > other relatives > persons of same coterie > persons of same race, nation, color, etc. > one's own dog, horse, cat, cow, etc. > other domestic mammals > wild mammals > other vertebrates > invertebrates > plants with capability of movement > other plants > non-living objects.

Fictional pain, portrayed in play or story, whether presented as physical pain or psychological distress, produces a fictional psychological reaction in the observer. Even if accompanied by the normal psychosomatic emergencies, namely tears and convulsions (sobbing), it is ordinarily accepted as pleasurable.

Sympathy is the general term for the psychological reaction in a person who observes (infers) real pain in another person or being (*vide supra*). Sympathy depends on an internal image of what is externally observed. The image is amended and polished by the personality of the observer. The image and the sympathy induced are quite independent of the truth or falsity of the inference about the physical pain suffered by another.

Courage is the refusal to let pain deter or deviate one from one's purpose or preferred way of life. Courage also lessens the psychosomatic concomitants of pain in the sufferer, and so reduces the quantity of sympathy that others feel obligated to. The observers are grateful for this. Courage extends into the future when pain is only threatened. This is essential, but what we are talking about here is pain present, not pain anticipated.

Admiration for courage is universal, and no wonder! The courageous fighter will win the fight, and enough courageous warriors will win the war *for us!* Those who bear their pain courageously spare our sympathy by that much. We find more pleasure in admiration than in sympathy (well, most of us do).

Self respect is enhanced in the courageous sufferer by the admiration of those observing his pain and his courage. The courageous person therefore reaps two rewards—(1) personal, in the diminution of the unpleasant psychosomatic emergencies produced by the pain, and (2) social, in the admiration of his friends and the approbation of Society.

Cruelty

Cruelty is something that accompanies the infliction of pain. It is an attribute of the instrument, whether person or tool. The pain itself may be called cruel, but that is a poetical extension of the meaning. It is quite usual to call the surgeon's

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EDITOR'S NOTE: The author of this essay was for many years professor and head of the Department of Radiology at Stanford University School of Medicine, posts from which he is now retired. An original and imaginative thinker, he is one of the West's most distinguished radiologists, an excellent clinician and a teacher of wide renown. For the more than 20 years that he served on the Editorial Board of CALIFORNIA MEDICINE, his extraordinary skill and interest in clear, concise expression contributed richly to this journal's stature.

His background, his ability and the quality of the present essay make this latest contribution a most welcome one.

knife cruel, even though the surgeon is not called cruel. For most people, the surgeon's benign purpose and his presumed sympathy offset the cruelty implicit in his operation.

Antagonism to the cruel person is the normal psychological effect of the sympathy induced in the beholder. Failure to reveal such antagonism in proper circumstances is described as hardness of heart. At times the hardhearted observer is accounted cruel, a sort of guilt by association.

Enjoyable emotional reaction to cruelty, or just to pain, has already been mentioned in the field of fiction. But the contemplation of real pain can serve as a foil to increase the observer's own sense of well-being. The increase of this emotion to the degree called exultation should be looked on as pathological, or at any rate sinful. Sexual perversions in which sexual excitement and satisfaction are found only in the suffering of pain (masochism) or the infliction of pain (sadism) are well known in psychopathology.

Aggression. The infliction of pain in order to enjoy the emotional reaction is not limited to overt pathological states. It is usual in aggressive acts of all sorts. Peck order is worked out in any society by the infliction of pain, physical or psychological. This must be called graduated cruelty. It has become socially acceptable in many cultures and subcultures. Hazing is an example.

Punishment is the infliction of pain for the purpose of influencing action (usually social interaction). Lip service is always rendered to the ideal, that cruelty does not enter, or only to the degree necessary. Father, whipping his son, says, "This hurts me more than it does you." The psychological effects of the cruelty are usually not completely avoidable, however. We always suspect that the executioner has a black heart.

Vengeance is punishment taken into one's own hands. The punishment is inflicted in order to enjoy its psychological effect. Cruelty is therefore an essential part of vengeance and is universally seen to be immoral except in those coteries or cultures in which the relatives of an injured person are required to avenge the injury (feuding). In our Western culture, vengeance is generally believed to be injurious to the personality (sinful) as well as being against public policy. "Vengeance is mine," saith the Lord.[1] Crime should be punished by the State after proper trial and judgment.

Careless infliction of pain may be from mere hardness of heart or due to preoccupation. Pain inflicted incidental to other purposes is no doubt just as hard to bear as if inflicted intentionally. But the psychological repercussions are quite different. Our judgment about the morality or sinfulness of pain incidentally inflicted depends on the purpose and the circumstances.

Selfish pursuit of one's own purposes regardless of the consequences is in the same category. The defense is sometimes presented that the person, wrapped up in his own project, is no more careless of other persons' comfort than of his own. This is usually seen to be a pretty lame excuse.

Lack of sympathy or "emotional blindness" is sometimes the reason for failing to avoid inflicting pain on other persons. Hardness of heart is no more lovable, however, just because it is claimed to be innate, instead of being newly developed for the selfish occasion.

Physical obtuseness is often confused with hardness of heart. One does occasionally find persons whose pain threshold is high, both physically and psychologically. The image of another person's pain reflected in themselves is dim. They see the other person's pain as if "through a glass, darkly."[2] Proper social training could, no doubt, bring such a person to apply his "personal equation" as a correction to every observation and thus standardize it to the common social norm. Applied generally, this ideal has been called "a decent respect to the opinions of mankind."[3]

Intellectual lack of conviction of the reality of pain produced in another person is usually accounted not logical, but simply hardness of heart. Concerning pain in lower animals, however, it may be logically defensible. (See below under hunting and fishing, vivisection, etc.)

Egotism can so overwhelm all other feelings that the emotional response to the observation of pain in others remains subliminal. This is especially likely when the egotist has inflicted the pain and the submergence of sympathy is a technique for protecting his ego from blame. It is easier to deny the pain than to excuse the action.

Cool choice of actions that incidentally produce pain or that are actually designed to produce pain is seen where the purpose is conceived to be imperative. It is notorious in the use of torture to wring confession from accused persons. In the past it led to the choice of flagrantly painful punishment to deter others from criminal or from adverse political action. Many religious sects have used torture to expiate sin and to gain ultimate bliss for the tortured person. One can only guess what the emotional repercussions were on the men who worked the rack in the Spanish Inquisition or on the Englishmen who ordered St. Joan tortured and burned. The coolest anecdote is the one about Ivan the Terrible, who was interested in torture. In the Tower of London he was shown the wheel, with regret expressed that no suitable criminal was at hand to be broken on it. The story is that Ivan said, "Use one of *my* men. I wish to see the demonstration."

Hunting, fishing and trapping have the purpose of obtaining the bodies of wild animals for food or clothing. They necessarily injure the animals and by common inference cause them pain. Originally the infliction of pain was a matter of indifference, but for a long time now has excited sympathy in observers, and in many of the hunters.

It is a common practice to "put the animal out of its misery," that is, to kill the wounded animal, thus terminating the presumed pain and the hunter's sympathetic disquiet at the same time. Some states outlaw traps that maim but do not kill. Most fishermen stun the fish, as soon as caught, by a blow on the head, feeling that a fish flapping about out of water is "suffering." Crabs and lobsters are caught without maiming them and are kept alive to preserve their food value. Controversy rages about the best way to kill with the least pain. The usual practice of throwing crabs into boiling water produces violent movements of their appendages, apprehended as evidence of severe pain. To put the crab in cool water and warm it gradually to boiling produces no such violent movement and is accounted "humane." No physiological experiments purporting to prove the absence of pain have come to my attention. Most states have laws regulating the way large animals are to be killed in abattoirs. A blow on the head or the severance of the spinal cord at the foramen magnum is considered "humane," that is, producing a minimum of pain.

All these things show the force of man's emotional reaction to observation of (presumed) pain in animals or the knowledge of it. The infliction of an injury is considered cruel and engenders a feeling of guilt in many persons. The intensity of feeling is so great in some persons that guilt is excited by eating flesh and even by wearing furs, because the animal has had to suffer pain. To protect their souls, such persons become vegetarians. Many of them know that their motive is sentimental and illogical. It would be cruel to tell such a person how silkworm chrysalides are boiled before winding off the silk, in order to see if he would logically eschew silk as well as fur.

Much has been written about the morality of hunting and fishing. If these activities are seen to hurt the feelings of people in general to a sufficient degree, one can presumably make an objective judgment of immorality. One suspects that the complaint is more usually based on the conviction that hunting and trapping are sinful—that "obviously" the hunter's personality is changed, that is, his heart is hardened, by the necessary repeated denial of the sympathy that would normally be excited by his cruel acts. This is not obvious to everyone. There are other influences effective to diminish the outward show of softer sentiment in hunters and trappers. They necessarily adapt to hardship in the chase, even to severe hardship in walking a long trapline in a cold winter. People who consider themselves physically and mentally (emotionally) "tough" are quite generally intolerant of the weaknesses that they observe in those persons whom they consider "soft." This is a species of psychological aggression and quite naturally begets the only reaction readily available, namely to call the "tough" ones cruel and sinful.

Not a few people say that the cruelty is an essential part of the hunter's motivation. This, I believe, is slander, even though there can be little doubt that the successful hunter enjoys a feeling of power, engendered at least in part by the pain and death inflicted, and not entirely by the sense of something difficult accomplished.

Contests

All contests, in which one person wins and another loses, depend on the infliction of pain (at least the emotional pain of defeat) for their validity. In *prize fighting* and *professional wrestling* we can be sure that the reward to the spectator lies in vicarious assault. To some degree the spectator identifies himself with one of the adversaries and mirrors in himself the exultation of inflicting pain upon the other. This probably is true also of all "body-contact" sports—football and hockey at any rate. In other sports, too, the spectator "identifies" with the victor. Any cruel feelings aroused are the psychological concomitants of aggression, without necessarily involving physical injury and pain.

Enough has already been said about attribution of human feelings to lower animals to make it clear that similar arguments apply to dogfighting and cockfighting, bullfighting and other such sports.

Spanish *bullfighting* deserves closer analysis. No doubt the spectators do identify themselves with the *toreros*. But it is not certain that the infliction of pain is the source of the *afficionado's* addiction. We are told that what the Spaniard admires is courage. (As who does not?) What he transfers to himself is the matador's skill and grace and above all his courage. The bull is not merely there to suffer. The bull is an essential actor in this parade of courage. The Spanish believe that nothing can exceed the nobility of a brave bull. "The bravery of a truly brave bull is something unearthly and unbelievable."[4]

Conclusion

Cruelty is not an attribute of pain, but of the thing or person that produced the pain, if it is perceived as cruel. Thus cruelty requires a witness. The pain can stand alone and so can the infliction of it. There is of necessity a witness there—the sufferer, supposing it is a man who's hurt. But if it's an animal, the human witness must be an onlooker. Anyhow it must be clear that no witness, no cruelty. Cruelty lies in the heart of the beholder just as beauty is said to lie only in his eyes.[5]

Objectively, the fact of cruelty is ordinarily established by the emotion of antagonism to the thing that causes the pain. Cruelty cannot, therefore, be objectively defined. Whatever you feel to be cruel *is* cruel. All we can say is that certain things are perceived as cruel by many persons and for such persons the emotional reaction is real enough. We ought to be careful not to inflict this upon them. But what is not felt to be cruel among the coterie that observes it or knows about it, is not cruel for those who do not observe it or know about it.

The antivivisectionists' hearts are wrung by sight or knowledge of pain suffered by a dog or other animal subjected to surgical or other injury. Knowing what this does to their own hearts, they believe that it must be doing the same thing to the heart of the experimenter. Consequently it is injuring the experimenter's personality, is antisocial, and should be stopped.

The antivivisectionist's mistake is in putting so much confidence in analogies. He knows what pain he would feel if the operation in question were performed upon himself. He knows what sympathy he would feel if a personal friend suffered so. He knows what guilt he would feel, or ought to feel, if he were the one to inflict the injury. Therefore, he argues, the experimenter should feel a like degree of guilt. If he doesn't, it is because his heart has become hardened. If he is past redemption, too bad! But at least young scientists should be saved from this disaster.

But in truth the experimenter does not feel this guilt. What the antivivisectionist refuses to face is the fact of his great good fortune that the experimenter can work free of guilt and so continue to make discoveries that enlarge man's understanding of the world we live in, and which are regularly put to work increasing the well-being of everyone (including the antivivisectionist).

One last quotation: Under a sketch of dogs in an experimental laboratory—

> *"For pity's sake, stop!"*
> *"For humanity's sake, go on!"*[6]

ROBERT R. NEWELL, M.D.
San Francisco

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2. I Corinthians 13: 12.
3. Declaration of Independence.
4. Hemingway, E.: Death in the Afternoon, Charles Scribner's Sons, New York, 1932, page 113.
5. Wallace, Lew: The Prince of India, Book III, Chpt. 6, page 178 (Beauty is altogether in the eye of the beholder).
6. Life: About 1914 (when it was its old self—a magazine of humor, and a fighter against vivisection).

California Medical Association

NOTICES AND REPORTS

Percodan on Triplicate

The Background of the New Law

THE TRIPLICATE prescription form as used in California and Illinois has been useful in two ways: First to prevent forgeries of prescriptions for hard narcotics, and second to educate the medical profession as to the addicting liabilities of these compounds.

In the 1963 session of the California Legislature, bills were introduced which would have placed Percodan on the triplicate form.

The bills were introduced on behalf of the Attorney General of the state representing law enforcement and the position taken in these bills was that the problem of forgeries was a real one and that this could be largely eliminated by use of the triplicate prescription. The bill was supported by Governor Edmund Brown, by law enforcement agencies generally, and by the California Medical Association.

The position of the California Medical Association was that the compounds should be placed on the triplicate form for a two-year period, and at the end of this time a second look would determine whether or not this had been a good idea and should be continued or whether the problem had been magnified somewhat and continuation should prove to be unnecessary.

In any event the bill was opposed by Endo Laboratories, Inc., on the basis that the problem was not great and that placing the product on the triplicate form would magnify the addiction liability in the minds of the physicians so that they would then not prescribe it even though its use in a particular case was reasonable and legitimate.

The Endo company did not at all condone the abuse of the product, but felt that the abuse was minimal.

The opposing point of view was that the narcotic ingredient—namely, oxocodone—was indeed highly addicting and even though it might be mixed with other ingredients which might negate the addicting liability, the addicting liability was still substantial; therefore, a reasonable position was to require the triplicate form.

As I appeared at the hearings at this time, it was apparent that there was much honest difference of opinion, and documentary evidence of it either way was not entirely clear-cut; there was a "gray zone," although the CMA proposal of a trial period of two years seemed reasonable enough.

In any event the proposed legislation did not pass and Percodan remained available on an ordinary prescription blank. At the 1965 session of the Legislature the bill was reintroduced.

The Endo company changed its position, stating that they felt that the matter was one in which they should not be involved lest the company be accused of self-interest, but one that should be settled by the representatives of medicine and law

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enforcement, with the final settlement naturally being then accomplished by the legislative process after the evidence had been weighed.

A bill was introduced which would place Percodan on triplicate; and after hearings had been conducted and the usual legislative processes satisfied, the bill passed and was signed by the Governor.

The Endo company did not oppose the bill at the most recent session and had a very constructive attitude; namely, that the company had made its position clear at the previous hearings, had nothing to add and felt that the matter was now a legislative one and should be settled by the legislative process.

Beginning September 15 of this year, the triplicate form will be required for prescription of Percodan, but one facet of this situation remains undetermined: It has to do with the Endo company's position that placing the drug on triplicate would create in the minds of physicians so strong a suspicion of the possibility of addiction that they would no longer prescribe it for patients for whom it was legitimately indicated. Percodan is a short-acting pain-relieving drug which is highly effective in relieving short-acting problems of pain such as dental problems, postoperative pain and the like; and the position of the CMA Committee on Dangerous Drugs is that physicians can be relied upon to use reasonable discretion in prescribing the drug.

The compound remains the same as before and the indications for its use are the same; the only change is that one more carbon copy of the prescription is required. Time will tell whether the misgivings of the Endo company are well grounded or my own optimism as to the judicious attitude of the medical profession in California will be justified.

It is hoped that placing Percodan on triplicate will not frighten physicians away from using it where it is needed but will merely alert him to the fact that he is indeed dealing with a drug with addiction liabilities and will not use it in the treatment of long-term illness such as arthritis, or in the treatment of the menopause or for unstable persons in whom he may be creating more problems than he solves.

In any event it is hoped that the physicians in California will be made aware of the fact that this legislation was not adopted capriciously and in a few years documentary evidence may well be available as to whether or not the law is needed.

WM. F. QUINN, M.D.
Chairman, Committee on Dangerous Drugs

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In Memoriam

Bailey, Frank W., Canoga Park. Died July 8, 1965, in Northridge, aged 64, of myocardial infarction. Graduate of Rush Medical College, Chicago, Illinois, 1939. Licensed in California in 1941. Doctor Bailey was a member of the Los Angeles County Medical Association.

◆

Bickel, Elsa F., San Francisco. Died July 25, 1965, in San Francisco, aged 49, of cerebral vascular accident. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1941. Licensed in California in 1941. Doctor Bickel was a member of the San Francisco Medical Society.

◆

Burnham, Clark James, Jr., Berkeley. Died July 28, 1965, in Berkeley, aged 65. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1931. Licensed in California in 1931. Doctor Burnham was a member of the Alameda-Contra Costa Medical Association.

◆

Byron, Ralph Louis, Los Angeles. Died July 18, 1965, in Duarte, aged 82, of perforated esophagus. Graduate of the College of Physicians and Surgeons, Los Angeles, 1908. Licensed in California in 1908. Doctor Byron was a member of the Los Angeles County Medical Association.

◆

Dean, William I., Jr., Los Angeles. Died July 26, 1965, in Los Angeles, aged 42, of heart disease. Graduate of Marquette University School of Medicine, Milwaukee, Wisconsin, 1953. Licensed in California in 1954. Doctor Dean was a member of the Los Angeles County Medical Association.

◆

Devin, Stephen Bernard, San Gabriel. Died June 11, 1965, in Oceanside, aged 60, of a coronary. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1932. Licensed in California in 1933. Doctor Devin was a member of the Los Angeles County Medical Association.

◆

Ducote, Ogden Louis, North Hollywood. Died July 30, 1965, in Burbank, aged 39, of cirrhosis of liver. Graduate of Louisiana State University School of Medicine, New Orleans, 1951. Licensed in California in 1952. Doctor Ducote was a member of the Los Angeles County Medical Association.

◆

Edwards, William McEwen, Sr., San Rafael. Died July 22, 1965, in Terra Linda, aged 85. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1903. Licensed in California in 1928. Doctor Edwards was a retired member of the Marin County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

◆

Forbes, Harvey James, San Marino. Died March 10, 1965, aged 84, of pneumonia. Graduate of the University of Illinois College of Medicine, Chicago, 1903. Licensed in California in 1910. Doctor Forbes was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Gaines, William Stewart, Red Bluff. Died July 7, 1965, in an airplane crash near Red Bluff, aged 41. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1949. Licensed in California in 1949. Doctor Gaines was a member of the Tehama County Medical Society.

◆

Luckie, James Buckner, Pasadena. Died July 14, 1965, in Pasadena, aged 77. Graduate of the University of Colorado School of Medicine, Denver, 1913. Licensed in California in 1915. Doctor Luckie was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Mietus, Aloysius C., Los Angeles. Died July 16, 1965, in Los Angeles, aged 50, of pneumonia. Graduate of Marquette University School of Medicine, Milwaukee, Wisconsin, 1938. Licensed in California in 1946. Doctor Mietus was a member of the Los Angeles County Medical Association.

◆

Nielsen, Robert F., Torrance. Died July 20, 1965, in Torrance, aged 49. Graduate of the University of Southern California School of Medicine, Los Angeles, 1942. Licensed in California in 1942. Doctor Nielsen was a member of the Los Angeles County Medical Association.

◆

Porter, Alfred Lamar, Los Angeles. Died July 6, 1965, in Los Angeles, aged 52, of cancer. Graduate of the University of Arkansas School of Medicine, Little Rock, 1939. Licensed in California in 1942. Doctor Porter was a member of the Los Angeles County Medical Association.

◆

Sheets, Oscar Bertram, Forest Falls (San Bernardino County). Died March 3, 1965, aged 90, of arteriosclerosis. Graduate of Fort Wayne College of Medicine, Indiana, 1900. Licensed in California in 1921. Doctor Sheets was a member of the Los Angeles County Medical

Association, a life member of the California Medical Association, and a member of the American Medical Association.

✣

Smith, Dorothy Johnstone, Hanford. Died July 6, 1965, in Hanford, aged 42. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1948. Licensed in California in 1948. Doctor Smith was a member of the Kings County Medical Society.

✣

Smith, Edwin Jefferson, Diamond Bar. Died July 15, 1965, in Pomona, aged 75. Graduate of the State University of Iowa College of Medicine, Iowa City, 1922. Licensed in California in 1932. Doctor Smith was a member of the Los Angeles County Medical Association.

✣

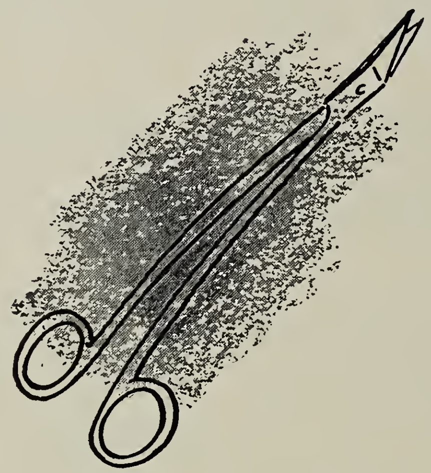
Thompson, William Benbow, La Canada. Died July 9, 1965, in Los Angeles, aged 74, of a ruptured aortic aneurysm. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1916. Licensed in California in 1916. Doctor Thompson was a member of the Los Angeles County Medical Association.

✣

Tyler, Lloyd G., San Rafael. Died June 10, 1965, in San Rafael, aged 67, of lymphosarcoma. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1928. Licensed in California in 1928. Doctor Tyler was a retired member of the Marin Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

Welbourn, Pina M., Van Nuys. Died July 12, 1965, in Van Nuys, aged 82, of cerebral thrombosis. Graduate of Eclectic Medical College, Cincinnati, Ohio, 1907. Licensed in California in 1907. Dr. Welbourn was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



PUBLIC HEALTH REPORT

MALCOLM H. MERRILL, M.D., M.P.H.
Director, State Department of Public Health

A NEW LABORATORY TEST being routinely provided in several areas of California portends great changes in the use of serologic procedures for the detection of syphilis.

This development is the Fluorescent treponemal antibody absorption (FTA-ABS) test. Technical success in developing a reliable absorbing agent by the department's Microbiology Laboratory has made it possible to utilize this test on a routine basis in many health department laboratories in California.

Although several FTA procedures have been publicized recently, little has appeared in the literature to help the physician understand their use as well as their limitations. The FTA-ABS is precise and reproducible and has the same significance as the TPI test. FTA-ABS has a particular advantage over the TPI test, as it becomes reactive earlier in the course of the disease.

In pregnancy, for example, determination of a new infection can be made much earlier by the FTA-ABS test than with TPI procedures. The FTA absorption test also remains reactive in late cases. Other advantages of the test are simplicity and ease of performance, reproducibility and lower cost.

Because of the relative ease of performance of the FTA-ABS test, it is not necessary to apply the restrictions for the submission of specimens which have been applied to the TPI test by the State Laboratory.

Use by local laboratories can be anticipated when commercially prepared reagents become available and when the test becomes popular enough to be utilized in quantity.

For one major reason there is little likelihood that the FTA-ABS test will replace the VDRL. Like the TPI test, the FTA absorption test cannot measure the efficacy of treatment. Titred VDRL testing will remain the method of choice for follow-up of treated cases. A reactive FTA-ABS test indicates definite exposure to pathogenic treponemes (syphilis, yaws, pinta, bejel) at some time in the patient's life and may persist even after adequate therapy.

Such persistence of antibody is not unique to the treponematoses. The tuberculin reaction is a similar example of an immunological test which may remain positive for a prolonged period, irrespective of therapy and with absence of active disease.

In view of influenza's two to three-year periodicity, increased occurrence of the disease may be expected in the coming season. Although Type A viruses may predominate in 1965-66, the presence of Type B in this country and its prevalence in Europe last season increases the expectation of Type B outbreaks in the United States this year.

Annual immunization is generally recommended for persons of various categories in which the mortality from epidemic influenza is high. Such groups include: persons at all ages who have chronic debilitating disease; patients with rheumatic heart disease, especially those with mitral stenosis; patients with other cardiovascular disorders; patients with chronic bronchopulmonary diseases; patients with diabetes mellitus and Addison's disease. Persons in older age groups also should be included. During three successive recent epidemics a moderate increase in mortality has been demonstrated among persons over 45 years of age, and a decided increase among those over 65.

It is to be noted that some increased mortality was observed among pregnant women during the 1957-58 influenza A2 epidemic. It has not, however, been demonstrated in subsequent years.

Vaccination should begin as soon as practicable after September 1 and ideally should be completed by mid-December. It is important that immunization be carried out before influenza occurs in the immediate area since there is a two-week interval before the development of antibodies.

WOMAN'S AUXILIARY

to the California Medical Association

Community Service

"Seek to Serve," this year's theme of the Woman's Auxiliary to the California Medical Association, is especially the goal of the auxiliary's Community Service program.

Service being more effective when we pool resources, we shall continue to group under Community Service those committees whose work deals with the community at large. These include Mental Health, Rural Health, Safety, Disaster Preparedness, Problems of the Aging and GEMS (Good Emergency Mother Substitutes)—our baby-sitting course.

We are very proud of our record of service for the past year. Eight counties reported programs in Health Problems of the Aging. Shasta-Trinity County with the assistance of teen-agers, conducts a new program of working with patients in the local convalescent hospitals. The teen-agers play games with the patients, do their hair, sew for them, have classes in arts and crafts, read to them, provide rides, have songfests and even a monthly birthday party. San Francisco County is celebrating its fifth year of Meals on Wheels.

Seven counties reported activity in Rural Health ranging from school projects to blood banks. The Santa Cruz Auxiliary has shown safety films to every high school and junior high school in the county. At county fairs there have been anti-quackery booths, safety booths and immunization booths. Butte-Glenn County had its first Health Fair, where for three days free tetanus immunizations and displays were offered.

Twelve counties reported having committees on Mental Health. Ten gave donations. Mendocino-Lake County raised $1,100 for its sheltered workshop by staging its Silver Ball. Imperial County Auxiliary is working with its Medical Society to establish a Mental Health Clinic under the Short-Doyle program.

Seven counties had Civil Defense programs at their meetings. Marin County is planning a first aid course for its members. Los Angeles County had a five-county mock exercise in Civil Defense. Napa County sponsored a panel program on Disaster Preparation to which the public was invited. The speakers included the director of the Napa State Hospital, the county public health officer, the president of the county medical society and a state Civil Defense representative. Fresno County Medical Society and Auxiliary are organizing a Disaster Plan for this community.

Nineteen counties had safety programs. San Francisco County conducted a seat belt campaign with posters in all municipal vehicles and at bridge toll stations. Napa County is distributing pamphlets through the Welcome Wagon to all newcomers. Marin County produced a film on smoking called "Too Tough to Care," which Santa Clara District II purchased. The film has been offered to schools and organizations in Santa Clara.

Ten counties have a GEMS program that has us bursting our buttons. In California this year 5,515 girls and boys will receive GEMS diplomas. Los Angeles County leads with 4,000 diplomas awarded. Orange County gave 450, and Santa Clara District I 350. San Mateo County has 200 graduates. Los Angeles County has been recognized nationally for its program with coast to coast television, newspaper and magazine coverage. The Los Angeles Auxiliary also produced two new films on GEMS this year.

In addition to those projects already mentioned, five counties have Homemaker Services, six help the handicapped, one has a Youth Fitness program, six had programs on Medicine and Religion and two gave awards to a lay person for outstanding community service. Members of the Humboldt-Del Norte County Auxiliary spent many volunteer hours helping the Medical Society and the Salvation Army during the recent flood disaster, and in several counties the Auxiliary is completely responsible for the Blood Bank in its area.

You can be very proud of our service to the community. Though each of us carries a small brush, we have painted a very large canvas.

Mrs. John Fittipoldi, Jr.
Community Service Chairman

INFORMATION

Preparation for Medicare

A Report from the Washington office of the American Medical Association

Health, Education and Welfare officials are drafting rules and regulations for operation of the new Social Security medicare law.

The new law provides for persons 65 years and older a basic hospitalization plan financed with Social Security taxes and a subsidized, voluntary, supplementary medical insurance program. Both programs will start July 1, 1966.

The existing Kerr-Mills program of medical assistance to the needy and near-needy aged is expanded and combined with all the other federal-state medical assistance programs into one plan with simplified administration, a uniform grant formula, specified benefits and minimum eligibility requirements.

Self-employed physicians are brought under Social Security retroactive to January 1, 1965. They will be required to pay next April $259.20 each in Social Security taxes for this year. The tax will go up to $405.90 for 1966 and rise over the years to $514.80 by 1987. Physicians were the last profession to be covered by Social Security and the only group to be forced into the system over the protests of its professional organization.

Coverage and liability for taxes for interns and residents will not begin until January 1, 1966.

The new law also increases Social Security cash benefits by an average of 7 per cent, retroactive to January 1, 1965.

To finance the new health care programs and the increase in cash benefits, both the Social Security tax base and tax rates will be increased. The tax base will be increased from the present $4,800 of workers' annual pay to $6,600 on January 1, 1966.

Additional Social Security Personnel

Arthur E. Hess, who has been with the Social Security Administration since 1939 and in charge of disability insurance since 1954, has been named to head up the new SSA Bureau of Disability and Health Insurance to handle the medicare program. A spokesman said the SSA, which now has 35,000 employes, will add between 7,000 and 8,000 more in the next year to administer the program.

President Johnson went to Independence, Mo., to sign the legislation (H.R. 6675) July 30 in the presence of former President Harry S. Truman who 20 years ago proposed in his legislative program a national medical insurance plan for all ages financed by higher Social Security taxes.

Commenting on the medicare program becoming law, F. J. L. Blasingame, M.D., executive vice president of the AMA, said in Chicago:

> We will watch developments in this new program and offer constructive suggestions, both to Congress and to the administrators of the program, in the interest of the maintenance of the highest quality of medical care.
>
> President Johnson has requested that we meet with officials of the Department of Health, Education and Welfare on the development of rules and regulations.
>
> Following our conference with Mr. Johnson on Thursday (July 29), initial meetings were held with HEW Secretary Anthony Celebrezze, exploring arrangements for AMA and HEW review of projected regulations and of problems of administration and interpretation of the law.
>
> The President also asked that we report back to him in two months on our progress.

The White House conference between Johnson and 11 top AMA elected and staff officials, developed from an action of the AMA House of Delegates in New York last June. The House approved a resolution including the following two resolves:

> *Resolved,* That this House of Delegates restate its offer to meet with the President of the United States through our Legislative Task Force to discuss proposed medical care legislation with a view to safeguarding the continued provision of the highest quality and availability of medical care to the people of the United States . . .
>
> *Resolved,* That the American Medical Association strongly urge those branches of the government interested in the formulation, the enactment, and the implementation of laws which deal with the provision of professional medical services to the public to seek and utilize the advice and assistance of the physicians who will render such services. Such advice and assistance should be received through our chosen representatives, the officers of the American Medical Association . . .

AMA-HEW Conference

The first AMA-HEW conference on medicare at the staff level was held in Washington a week after the program became law.

HEW was consulting representatives of the American Hospital Association even before the legislation was signed into law.

The Social Security Administration, in administering the basic and supplementary health care programs, will utilize Blue Cross, Blue Shield, private health insurance carriers or combinations of them as "fiscal intermediaries." At this writing, they had not been named.

HEW said the physician will be the key figure in the basic as well as the supplementary program. He will decide upon admission to a hospital or posthospital extended care facility, order tests, drugs and treatment, including home health services, and determine the length of stay, HEW said.

As to length of stay, however, hospitals and extended care facilities participating in the program will be required "to have in effect a utilization review plan providing for a review of admissions, length of stays and the medical necessity for services provided."

Such reviews "would ordinarily be carried out by a staff committee of the institution," and include other professional personnel such as registered nurses and medical social workers in addition to two or more physicians.

As an alternative, HEW said, reviews could be conducted by a similar group outside the institution—preferably one established by the local medical society and some or all of the hospitals and extended care facilities in the locality.

Under the supplementary program, the patients could pay the doctor and be reimbursed 80 per cent of a "reasonable" fee. If the doctor so chose, he could let the patient assign to him the amount the patient would be reimbursed. If payment is on the basis of an assignment, the "reasonable" fee would have to be accepted as the full payment. If the physician receives payment only directly from the patient, he can charge the amount he chooses regardless of what is determined to be a "reasonable" fee.

In determination of a "reasonable" fee, HEW said, the supplementary insurance carriers, must "assure that the charge on which the reimbursement is based is reasonable and is not higher than the charge used for reimbursement on behalf of the carriers' own policyholders or subscribers for comparable services and under comparable circumstances."

Summary of Law's Health Care Provisions

BASIC PROGRAM

Hospitalization

Up to 90 days in each spell of illness. The patient pays the first $40 of hospital costs. If he stays more than 60 days, he pays $10 for each additional day up to the 90-day limit. A spell of illness starts with the first day of hospitalization and ends when the patient has spent 60 consecutive days without hospital or nursing care.

The hospitalization covers room and board, prescribed drugs while hospitalized and other services and supplies except private duty nursing and services of physicians other than interns or residents in training. Christian Science sanatoriums and psychiatric hospitals are included. There is a lifetime limit of 190 days in a psychiatric hospital.

Nursing Home Care

Up to 100 days in an extended care facility in each spell of illness after a stay of at least three days in a hospital. There is no charge to the patient for the first 20 days. The patient pays $5 for each day above 20, up to the 100-day limit.

Home Nursing

Up to 100 visits by nurses or technicians in a one-year period following the patient's discharge from a hospital or extended care facility. The services furnished must be in accordance with a program set up and periodically reviewed by a physician.

Diagnostic Services

Tests and related diagnostic services, other than those performed by physicians, that are normally provided by hospitals to out-patients. The patient pays $20 of the charge for each diagnostic study provided by the same hospital in a 20-day period. The patient pays 20 per cent of the charges above $20.

SUPPLEMENTARY PROGRAM

Persons enrolling in this program will pay $3 a month in premiums. The federal government will match this with a payment of $3 a month for each participant. The federal share, about $600 million a year, will come from general tax revenues. The insurance supplements the basic program by covering most other major medical expenses except those for dental services, medicines and drugs.

A participant in the program pays $50 of his annual costs for the services and supplies. He also pays 20 per cent of the annual costs above $50 while the program pays 80 per cent.

The coverage includes:

Physicians' services, including surgical, whether performed in a hospital, clinic, office or home.

Up to 100 home nursing visits each year in addition to those allowed under the basic program and without any requirement for previous hospitalization.

Various services and supplies, whether provided in or out of a medical institution, such as x-ray and other diagnostic tests, radiological treatments, surgical dressings, splints, casts, iron lungs and other specified prosthetic devices, artificial arms, legs and eyes and ambulance service.

WELFARE AID

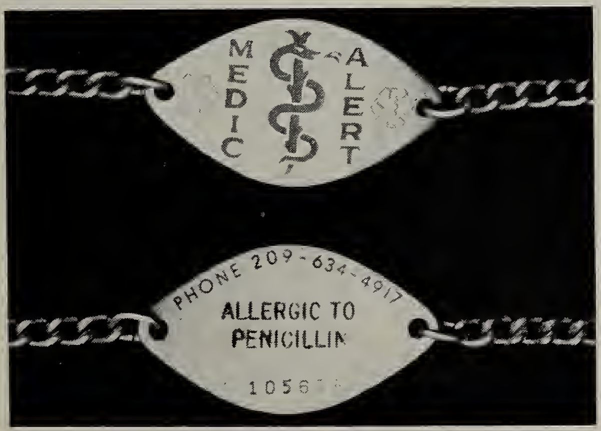
The bill authorizes increases of about $400 million in annual federal grants to states for public assistance (relief of the needy) and other welfare programs. It consolidates the Kerr-Mills medical assistance program with five related programs and sets federal standards for the scope of benefits and eligibility of beneficiaries.

A new program of health care for children in impoverished families is established, with $185 million in grants authorized for the first five years. Grants for maternal and child health services and aid to crippled children are raised in four steps from the present level of $80 million to $120 million in 1970.

By revising the general formula for public assistance grants, the bill raises annual federal authorizations by $150 million.

Look for This Emblem

The medic alert emblem has been developed to meet the need of 40 million Americans whose hidden medical problems should be known in emergency. It speaks for the wearer when he is uncommunicative or unconscious.



The medical profession has long been aware of the hazards of the violent and sometimes fatal reactions to drugs or medications to which some patients are hypersensitive. Physicians too often are faced with complications of injury or illness as a result of being unaware or uninformed that the unconscious patient has, say, diabetes or is taking an anticoagulant or cortisone.

A physician whose daughter nearly died 10 years ago due to a severe anaphylatic reaction to a skin test to determine if she had allergic sensitivity to tetanus antitoxin, realized that another such ocurrence could well be fatal. Determined to provide some way of making his daughter's allergic state known in emergency, he developed a medical identification system. It soon became known as the Medic Alert Foundation International, a nonprofit, charitable, tax deductible organization, whose services are used by more than 125,000 people throughout the world.

The Medic Alert emblem of durable sterling silver or stainless steel is designed for constant wear about the neck or wrist. On one side is the staff of Aesculapius, flanked by the words "Medic Alert" in red enamel. Recently the AMA symbol for medical identification was added. This action was taken at the suggestion of Medic Alert's National Medical Advisory Committee under the co-chairmanship of Dr. David A. Wood of San Francisco and Dr. James Murphy of Fort Worth, Texas.

The AMA does not sell or distribute emblems bearing its symbol. It merely adopted the design and is recommending its use on identification devices. To quote AMA's Dr. Donald Dukelow, "The symbol is meant to complement rather than to displace existing medical identification."

On the reverse side of the emblem is engraved the wearer's immediate medical problem such as "diabetes," "taking anticoagulants," "allergic to penicillin," and "neck breather." Each emblem is serialized and bears the number of the central answering file. Under the serial number is filed the wearer's name, whom to notify in emergency, his physician's name and address, and further pertinent medical information. The answering service receives collect calls 24 hours a day to supply this information to authorized persons giving definitive medical care or first aid to members of Medic Alert.

The American Academy of General Practice, National Sheriffs, International Chiefs of Police and Fire Chiefs and many state and county medical associations, health associations and civic clubs have endorsed the Medic Alert's public service program. Thirty of the national and international airlines are including knowledge of Medic Alert identification in the training program of their employees. Life underwriters associations all over the United States are sponsoring Medic Alert.

To date, sister organizations have been formed and are active in South Africa, Holland, Great Britain, Ireland, Canada, New Zealand and the Philippines. Medic Alert is registered in 17 other foreign countries.

To quote from the *Massachusetts Physician* of May 1964, "Instead of a confusion of devices and a multitude of promoters, the physician can safely recommend one nonprofit, tax-exempt association, the Medic Alert Foundation, International.

Further information and membership application forms may be secured by addressing Medic Alert Foundation, Turlock, California.

NEWS & NOTES

NATIONAL • STATE • COUNTY

ALAMEDA

A grant of $5,000 to the **Institute for Metabolic Research,** Oakland, for continued investigation into the relative merits of safflower and other vegetable oils in the diet has been made by the Safflower Council of the National Institute of Oilseed Products. The goal is to determine whether altering the kind and amount of fat consumed can lessen the risk of heart attacks and strokes.

The study, begun in 1963, is headed by Dr. Laurence Kinsell, director of the Institute.

LOS ANGELES

A $625,000 five-year grant for the **training of resident physicians in psychiatry** has been awarded by the National Institute of Mental Health to the USC School of Medicine's Department of Psychiatry, it was announced recently by Dr. Edward J. Stainbrook, professor and chairman of psychiatry.

SANTA CLARA

Robert G. Lindee has been appointed assistant dean for administration and assistant to the vice president for medical affairs of the **Stanford University School of Medicine.** The announcement was made by Dr. Robert J. Glaser, vice president for medical affairs and dean of the medical school.

Mr. Lindee has been associated with Dr. Glaser for the past five years, most recently as his assistant when he was president of Affiliated Hospitals Center, Inc. in Boston, and before that as his executive assistant when he served as vice president for medical affairs and dean of the University of Colorado Medical School.

A competition for a $250 award for the best manuscript submitted by a medical student, intern or resident on any subject pertinent to and concerning **occupational health** has been announced by the **Central States Society of Industrial Medicine and Surgery.** The contest closes at midnight on December 31, 1965.

A second competition, open only to residents in occupational medicine, is announced by the **Industrial Medical Association.** The award, consisting of an embossed scroll, will be presented at the Association's annual meeting to the author or authors of a paper published in the open literature on a subject germane to occupational medicine which is judged to be the most outstanding of those submitted. Reprints entered in the competition must be published during 1965 and submitted before January 15, 1966.

Complete contest rules may be obtained from: Industrial Medical Association, 55 East Washington St., Chicago, Ill. 60602.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

SEPTEMBER

September 16-December 9—**Medical Radio Conferences.** UCSF. Thursdays, 12:30-1:30 p.m.

September 16-December 9—**Teaching Clinics in Internal Medicine.** UCLA. Thursdays.

September 16-18—**Western Section, Association for Research in Ophthalmology Meeting.** Tahoe Alumni Center, Lake Tahoe (North Shore). Thursday-Saturday. Contact: Daniel G. Vaughan, M.D., University of California Medical Center, San Francisco 94122.

September 16-May 19—**Postgraduate Medical Lecture Series.** UCLA in San Bernardino and Riverside Counties. 3rd Thursday of each month. 18 hours. No fee.

September 18—**Cardiovascular Disease Symposium.** Jointly sponsored by Santa Barbara and Ventura Counties Heart Associations. Santa Barbara Biltmore Hotel. Saturday from 9:00 a.m. to 5:00 p.m. Contact: Wendell D. Klossner, M.D., chairman, Santa Barbara County Heart Association Symposium Committee, 1478 E. Valley Rd., Santa Barbara.

September 20-October 13—**Sacramento Valley Circuit Courses** presented by CMA in cooperation with UCSF. Dunsmuir: Mondays, Chico: Tuesdays, Auburn: Wednesdays. $30.: Spring and Fall. Spring Courses: February 21-March 16, 1966.

September 20-May 23—**Radiological Physics.** UCSF. Mondays. $150.

September 21-October 26—**Specific Syndromes Associated with Mental Retardation.** UCSF at Sonoma State Hospital, Eldridge. Tuesdays. 12 hours. $10.

September 22-24—**Recent Advances in Internal Medicine.** UCSF. Wedneday-Friday. $60.†

September 22-December 15—**Psychotherapeutic Medicine for Non-Psychiatrists.** UCSF. Wednesdays.*†

September 23-October 28—**Preventive Psychiatry.** UCSF at Modesto State Hospital, Modesto. Thursdays. $10.†

September 25-26—**Child Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday-Sunday. 10 hours. $10.

September 25-26—**Manifestations and Therapy of Anxiety.** UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday. 9 hours. $7.

September 28—**American Academy of Pediatrics, California Section III, Annual Seminar on Epilepsy.** Town and Country Hotel, San Diego. Tuesday. 4 hours. $10. Contact: J. Richard Hill, M.D., 525 Hawthorn Street, San Diego.

September 29-30—**Los Angeles County Heart Association Annual Fall Symposium on Cardiovascular Disease.** Statler Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hours. Contact: Harold Miller, M.D., chairman, Professional Education Committee, 2405 West Eighth Street, Los Angeles 90057.

September 29-October 1—**San Francisco Heart Association Annual Postgraduate Symposium on Heart Disease.** Fairmont Hotel, San Francisco. Wednesday-Friday. 18 hours. Contact: Maurice Sokolow, M.D., chairman, Symposium Planning Committee, San Francisco Heart Assoc., 259 Geary Street.

OCTOBER

October 1-2—**San Diego County Heart Association Annual Professional Symposium on Heart Disease.** Town and Country Hotel, San Diego. Friday-Saturday. 8 hours. Contact: James E. Lasry, M.D., chairman, Professional Education Committee, 3545 4th Avenue, San Diego 92103.

October 1-2—**Urology.** UCSF. Friday-Saturday. $40.†

October 5-November 16—**Isotope Techniques in the Health Sciences.** UCSF. Tuesdays.

October 5-November 30—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesdays. 19 hours. $35.

October 6-27—**Basic Funduscopy in Internal Medicine.** USC. Wednesday evenings. 8 hours. $45.

October 7-9—**Obstetrics and Gynecology.** UCSF. Thursday-Saturday. $60.†

October 8-9—**Western Industrial Medical Association.** Hilton Hotel, San Francisco. Friday-Saturday. Contact: Christine Einert, M.D., 629 Euclid Avenue, Berkeley 94708.

October 9—**Conference on Uterine Cancer.** Co-sponsored by American Cancer Society, California Division, CMA Committee on Cancer and USC. International Airport Hotel, Los Angeles. Saturday, 9:00 a.m.-4:00 p.m. No fee. Contact: Cancer Coordinator, USC, Box 257, 1200 N. State Street, Los Angeles 90033.

October 9—**Immunological Disease and Infectious Disease in Children.** Children's Hospital Medical Center, 51st and Grove Streets, Oakland. Saturday. 7 hours. Contact: Children's Hospital Medical Center.

October 9-10—**Common Psychological Problems.** UCLA in San Bernardino. Saturday-Sunday.

October 9-10—**Cytology for Pathologists.** UCSF. Saturday-Sunday. $35.†

October 10-13—**Medicine and Religion.** UCLA Residential Conference Center, Lake Arrowhead. Sunday-Wednesday.

October 12—**Northeastern California Rheumatoid Foundation Seminar: Medical and Surgical Aspects of Arthritis.** Mercy Hospital, Sacramento, Tuesday. Contact: Harold B. Strauch, M.D., 4101 J Street, Sacramento.

October 12-November 16—**Neuropsychiatry in Daily Practice.** UCSF at Agnews State Hospital, San Jose. Tuesdays.*†

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts
for Postgraduate Course Information

CMA:	**California Medical Association** For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. PRospect 6-9400, Ext. 68.
LLU:	**Loma Linda University** For information contact: W. F. Norwood, Ph.D., Assistant Dean and Chairman, Division of Continuing Education, Loma Linda University School of Medicine, 1720 Brooklyn Ave., Los Angeles 90033, ANgeles 9-7241, Ext. 214.
PRES. MED. CTR.	**Presbyterian Medical Center** For information contact: Arthur Selzer, M.D., chairman, Education Committee, Presbyterian Medical Center, Clay and Webster Streets, San Francisco 94115. WEst 1-8000.
UCLA:	**University of California at Los Angeles** For information contact: Charles R. Smart, M.D., Assistant Director, Continuing Education in Medicine and Health Sciences, UCLA Medical Center, Los Angeles, 90024, 478-9711, Ext. 2114.
UCSF:	**University of California, San Francisco** For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, University of California Medical Center, Room 565-U, San Francisco 94122, 666-1692.
USC:	**University of Southern California** For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, USC School of Medicine, 2025 Zonal Ave., Los Angeles 90033, 90033, CApital 5-1511, Ext. 300.
STAN:	**Stanford University** For information contact: Roy Cohn, M.D., Associate Dean for Graduate Affairs, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto, DAvenport 1-1200.

*Fee to be announced. †Hours to be announced.

October 14-November 18—**Psychiatric Case Conferences-Section 7.** USC at San Diego County General Hospital. Thursday nights. 2nd session January 6 through February 10. 24 hours. $20 per session or $35 for both.

October 15-16—**Central Nervous System Infections.** UCSF. Friday-Saturday.*†

October 15-16—**Logical Glaucoma Therapy.** UCSF. Friday-Saturday. $50.†

October 16—**Imperial County Medical Society Program on Emergency Room Treatment.** Barbara Worth Country Club. Saturday. 8 hours. Contact: Imperial County Medical Society, El Centro.

October 18-22—**Pediatric Allergy.** UCSF. Monday-Friday. $125.

October 19-November 23—**Neuropsychiatry in Daily Practice.** Agnews State Hospital, San Jose. UCSF. Tuesdays. 12 hours. $10.

October 20—**Newborn Infant Care.** USC. Wednesday. 8 hours. $25.

October 20-April 20—**Basic Science Course in Ophthalmology.** UCLA. Wednesdays. Lecture: 49 hours, Lab: 31½ hours. $175 for full course.

October 22-24—**California Society of Internal Medicine Annual Meeting.** Hotel Del Coronado, Coronado. Friday-Sunday. Contact: Nancy V. Louw, executive secretary, California Society of Internal Medicine, 350 Post Street, San Francisco 94108.

October 23—**Endocrine and Metabolic Disorders.** UCSF at Childrens Hospital, San Francisco. Saturday. $15.†

October 23—**Obstetrics and Gynecology Annual Fall Seminar.** Auditorium of the Santa Clara County Administration Building, 70 West Hedding Street, San Jose. Saturday from 8:30 a.m. to 4:30 p.m. Contact: Howard W. Christopher, M.D., secretary, Shufelt Society of Santa Clara County, 621 E. Campbell Ave., Campbell.

October 23-24—**Practical Management of Surgical Problems.** UCSF at Franklin Hospital, San Francisco. Saturday-Sunday. $30.†

October 24-27—**California Academy of General Practice Annual Scientific Assembly.** Statler Hotel, Los Angeles. Sunday-Wednesday. 13 hours. Contact: Mr. William W. Rogers, executive secretary, California Academy of General Practice, 9 First Street, Room 900, San Francisco.

October 27-29—**American Thoracic Society Postgraduate Course on the Evaluation of Pulmonary Function.** Stanford University School of Medicine, Palo Alto. Wednesday-Friday. 24 hours. $75. $50 for ATS members. Contact: Rudy Glover, Tuberculosis and Health Association of California, 424 Pendleton Way, Oakland.

October 28-31—**Pacific Coast Fertility Society Annual Meeting.** Sahara Hotel, Las Vegas. Thursday-Sunday. Contact: Gregory Smith, M.D., 909 Hyde Street, San Francisco 94109.

October 29—**Kern County General Hospital Postgraduate Conference.** Kern County General Hospital, 1830 Flower Street, Bakersfield. Friday. 8 hours. Contact: George A. Paulsen, M.D., chairman, Postgraduate Conference Committee, Kern County General Hospital.

October 29-30—**Arthritis in Practice.** UCSF. Friday-Saturday. $40.†

October 29-31—**Southern California Psychiatric Society Annual Convention.** Santa Barbara Biltmore Hotel. Friday-Sunday. Contact: Ralph M. Obler, M.D., 11860 Wilshire Blvd., Los Angeles 90025.

NOVEMBER

November 3-4—**A Practical Approach to the Diagnosis and Treatment of Arrhythmias and Conduction Defects.** USC at Ambassador Hotel, 3400 Wilshire, Los Angeles. Wednesday-Thursday. 16 hours. $50.

November 5-6—**California Hospital Seminar on the Acute Abdomen.** California Hospital, 1414 South Hope Street, Los Angeles. Friday-Saturday. 12 hours. Contact: Kenneth L. Senter, M.D., Director of Medical Education, California Hospital.

November 5-6—**The Compensable Injury.** USC at Orthopedic Hospital, 2400 South Flower Street, Los Angeles. Friday-Saturday. 12 hours. $60.

November 5-6—**Comprehensive Medical Care and the Psychiatric Consultation.** UCSF. Friday-Saturday. $20.

November 5-6—**Diseases of the Biliary System.** UCSF. Friday-Saturday. $40.†

November 6-7—**Postgraduate Seminars in Psychiatry.** UCSF at Fresno Community Hospital, Fresno. Saturday-Sunday. $10.†

November 10—**The Southern California Annual Science Lecture of The American College of Physicians.** Statler Hilton Hotel, Los Angeles. Wednesday, 6:30 p.m. Contact: W. Philip Corr, M.D., Governor for Southern California, The American College of Physicians, 3660 Arlington Avenue, Riverside 92506.

November 11-13—**Gerontological Society.** Ambassador Hotel, Los Angeles. Thursday-Saturday. Contact: Mrs. Marjorie Adler, Gerontological Society, 661 S. Euclid, St. Louis 63110.

November 11-13—**Annual Western Institute on Epilepsy.** Kona Kai Club, Shelter Island, San Diego. Thursday-Saturday. $10. Contact: Manuel Barba, M.D., San Diego County Epilepsy Society, 1612 30th Street, San Diego 92102.

November 12-13—**Central Nervous System Infections.** UCSF. Friday-Saturday. $40.

November 12-13—**Kaiser Foundation Hospitals Symposium on Genetics.** Statler Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Herman Weiner, M.D., Permanente Medical Group, 1505 North Edgemont, Los Angeles 90027.

November 13-14—**First Annual Clinical Cancer Conference.** UCSF in cooperation with California Division, American Cancer Society. Friday-Saturday. $20.†

November 14—**Current Cancer Chemotherapy.** UCLA at Glendale Sanitarium—Annual Meeting. Sunday.*†

November 16-17—**Albert M. Snell Memorial Lectures.** Presented by the Palo Alto Medical Research Foundation. Palo Alto Medical Clinic Auditorium. Tuesday and Wednesday evenings at 8:00 p.m. Contact: Edward E. Daleske, assistant director, Palo Alto Medical Research Foundation, 860 Bryant St., Palo Alto.

November 17—**Santa Barbara Cottage and General Hospitals Program on Advances in Medical Practice.** Santa Barbara Cottage Hospital. Wednesday. 3 hours. Contact: C. A. Domz, M.D., 317 West Pueblo, Santa Barbara.

November 17-February 9—**Psychiatric Case Conferences-Section 2.** USC at Memorial Hospital of Long Beach. Wednesday evenings. 24 hours. $35.

November 19-20—**Fear and Pain Control: A Practical Approach.** UCSF. Friday-Saturday. $40.

November 19-20—**Musculoskeletal System: Congenital and Heritable Defects.** UCSF. Friday-Saturday.*†

November 23-February 15—**Psychiatric Case Conferences-Section 4.** USC at Valley Presbyterian Hospital, Van Nuys. Tuesday evenings. 24 hours. $35.

November 30-February 22—**Psychiatric Case Conferences-Section 5.** USC at Hawthorne Community Hospital. Tuesday evenings. 24 hours. $35.

DECEMBER

December 1—**St. Luke Hospital Annual Postgraduate Assembly.** St. Luke Hospital Staff Room, Pasadena. Wednesday. 8 hours. Contact: R. D. Miller, M.D., chairman, Annual Postgraduate Assembly, 615 East Union Street, Pasadena 91101.

December 1-4—**Ophthalmology Symposium: Retinopathy and Diabetes.** UCSF. Wednesday-Saturday.*†

December 1-March 2—**Psychiatric Case Conferences-Section 1.** USC. Wednesday evenings. 24 hours. $35.

December 1-March 2—**Psychiatric Case Conferences-Section 3.** USC at Santa Monica Hospital. Wednesday evenings. 24 hours. $35.

December 2-3—**Medicine Megalopolis.** USC at Ambassador Hotel, 3400 Wilshire Blvd., Los Angeles. Thursday-Friday. 16 hours. $25.

December 2-4—**California Society of Pathologists—Data Processing in Laboratory Medicine.** Disneyland Hotel, Anaheim. Thursday-Saturday. Contact: Weldon K. Bullock, M.D., 1200 N. State Street, Los Angeles.

December 2-4—**Microangiopathy of the Eye in Diabetes Mellitus.** UCSF. Thursday-Saturday. $75.

December 3-4—**Vectorcardiography.** UCSF. Friday-Saturday. $40.†

December 3-5—**Fluid and Electrolyte Balance.** USC at the Riviera Hotel, Palm Springs. Friday-Sunday. 15 hours. $60.

December 7-March 1—**Psychiatric Interviewing in Medical Practice.** USC. Tuesday evenings. 24 hours. $35.

December 8—**Tuberculosis and Health Association of Alameda County Annual Symposium-Seminars on Respiratory Diseases.** Co-sponsored by the Alameda-Contra Costa Academy of General Practice. Berkeley House Hotel/Motel, Berkeley. Wednesday. 6 hours. Contact: E. Ronald Riggall, M.D., chairman, 121 E. 11th Street, Oakland.

December 11—**Medical Emergencies.** Pres. Med. Ctr. Saturday. 8 hours. $30.

December 11-12—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton. Saturday-Sunday. $10.†

JANUARY

January 8—**Human Development and Birth Defects.** UCSF at Childrens Hospital, San Francisco. Saturday. $15.

January 18-April 12—**Medical Radio Conferences.** UCSF. Tuesdays, 12:30-1:30 p.m.

January 19—**Los Angeles County Heart Association Annual Midwinter Symposium.** Statler Hilton Hotel, Los Angeles. Wednesday. 6 hours. Contact: Harold Miller, M.D., chairman, Professional Education Committee, 2405 W. Eighth Street, Los Angeles 90057.

January 19—**Riverside County General Hospital Postgraduate Assembly.** Riverside County General Hospital. Wednesday. 12 hours. Contact: Harold A. Roth, M.D., Riverside County General Hospital, 9851 Magnolia Avenue, Riverside 92503.

January 19-April 20—**Psychotherapeutic Principles and Practice for Non-Psychiatrists.** UCSF. Wednesdays. $25.

January 19-May 18—**Teaching Clinics in Psychiatry.** UCLA. Wednesdays.

January 20-21—**New and Old Antibiotics.** USC. Thursday-Friday.*†

January 20-April 7—**Medical Radio Conferences.** UCSF. Thursdays, 12:30-1:30 p.m.

January 21-23—**A Time for Decision: The Biologic Crossroad.** UCSF. Friday-Sunday.

January 22—**Pediatric Cardiology Symposium.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 28—**Nuclear Medicine.** USC. Friday.*†

January 28-30—**Clinical Conference in Pediatric Anesthesiology.** Friday-Sunday. Contact: M. Digby Leigh, M.D., Childrens Hospital of Los Angeles, 4614 Sunset Blvd., Los Angeles 90027.

January 29—**Practical Proctology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 31-February 1—**Uroradiology.** UCLA. Monday-Tuesday.*†

FEBRUARY

Februrary 1-March 22—**Isotope Techniques in the Health Sciences.** UCSF. Tuesdays.

February 1-April 19—**Bedside Cardiology.** USC at Los Angeles County Hospital. Tuesdays.*†

February 2-4—**Aviation Medicine Seminars.** UCSF at Del Webb's Townehouse, San Francisco. Wednesday-Friday.

February 3-4—**SOUTHERN COUNTIES—Regional Postgraduate Institute presented by California Medical Association** in cooperation with USC School of Medicine. El Mirador Hotel, Palm Springs. "Hematology and Infectious Diseases and Antibiotics." Chairman: Robert M. Zweig, M.D., 3875 Jackson, Arlington.

February 4-5—**New Potentials in the Treatment of Common Diseases.** UCSF. Friday-Saturday.

February 4-March 11—**Psychiatry in Daily Practice.** UCSF at Mercy Hospital, Redding. Fridays.

February 7—**Medical Aspects of Well Being: Emotional Aspects of Rehabilitation.** UCSF. Monday.

February 9—**Symposium on Shock.** USC. Wednesday.*†

February 10-11—**Symposium on Endocrinology.** USC. Thursday-Friday.*†

February 10-12—**Pediatric Ophthalmology.** UCSF. Thursday-Saturday.

February 11-13—**American College of Physicians, Northern California and Nevada Regional Meeting.** Mark Thomas Inn, Monterey. Friday-Sunday. 10 hours. Contact: Roberto F. Escamilla, M.D., Governor, Northern California and Nevada Region, American College of Physicians, 897 Hyde Street, San Francisco.

February 12—**Surgical Emergencies.** Pres. Med. Ctr. Saturday. 8 hours. $30.

February 12-13—**Cystic Fibrosis.** UCLA. Saturday-Sunday.

February 12-13—**A Symposium on Hypnosis.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

February 12-13—**Law-Science-Medicine.** UCSF. Saturday-Sunday.

February 14-16—**Institute for Metabolic Research Dynamics of Endocrine and Metabolic Disease Annual Symposium.** Highland Hospital. $30. Contact: L. W. Kinsell, M.D., director, Institute of Metabolic Research, 2701 14th Ave., Oakland.

February 14-18—**American College of Chest Physicians—Clinical Application of Cardio-Pulmonary Physiology.** Ambassador Hotel, Los Angeles. Monday-

Friday. Contact: Alfred Goldman, M.D., program chairman, Suite 906, 9201 Sunset Blvd., los Angeles 90069.

February 14-18—**Course for Physicians in General Practice.** UCSF at Mt. Zion Hospital, San Francisco. Monday-Friday.

February 16-20—**Controversial Areas in Surgery.** UCLA at Palm Springs. Wednesday-Sunday.*†

February 18-19—**Pediatric Dermatology.** UCSF. Friday-Saturday.

February 18-20—**American College of Physicians Southern California Regional Meeting.** Biltmore Hotel, Santa Barbara. Friday-Sunday. Contact: W. Philip Corr, M.D., governor, 3660 Arlington Ave., Riverside 92506.

February 19-20—**Neuropsychiatry in Daily Practice.** UCSF in Salinas and Monterey. Saturday-Sunday.

February 20-23—**Current Concepts in Chemotherapy.** UCLA at Palm Springs. Sunday-Wednesday.*†

February 24-25—**Medical-Surgical Gastroenterology Conference.** USC. Thursday-Friday.*†

February 25-26—**Workshop on Hand Injuries.** Pres. Med. Ctr. Friday-Saturday. 12 hours. $75.

February 25-27—**Conference on Mental Retardation for Physicians.** UCSF. Friday-Sunday.

MARCH

March 2-3—**Los Angeles County Heart Association Annual Spring Symposium.** Statler Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hours. Contact: Harold Miller, M.D., chairman, Professional Education Committee, 2405 W. Eighth Street, Los Angeles 90057.

March 3-4—**Symposium on Diabetes.** USC. Thursday-Friday.

March 4-5—**Gynecological Problems for the Non-Gynecologist.** UCSF. Friday-Saturday.

March 4-5—**Operable Heart Disease.** Pres. Med. Ctr. Friday-Saturday. 16 hours. $35.

March 5-6—**The Knee.** UCLA. Saturday-Sunday.*†

March 5-6—**Sexual Conflicts and Adjustments.** UCSF at Herrick Hospital, Berkeley. Saturday-Sunday.

March 9-11—**Conference on Keratoplasty.** Pres. Med. Ctr. Wednesday-Friday. 21 hours. Contact: Jerome W. Bettman, M.D., 2400 Clay Street, San Francisco.

March 9-13—**Diagnostic Radiology.** UCSF. Wednesday-Sunday.

March 10-14—**Pulmonary Problems.** UCLA. Thursday-Sunday.*†

March 11-12—**Childrens Hospital Medical Center Annual Postgraduate Seminar and Clifford D. Sweet Lecture.** Childrens Hospital, 51st and Grove Streets, Oakland. 8 hours. $30 for 4 sessions or $10 per session. Contact: Childrens Hospital Medical Center, Oakland.

March 11-12—**WEST COAST COUNTIES—Regional Postgraduate Institute presented by California Medical Association** in cooperation with UCSF. Ojai Valley Inn, Ojai. "Indications for Surgical Intervention—The Difficult Decision." Chairman: George J. Wittenstein, M.D., 2235 Castillo, Santa Barbara.

March 12—**Cancer: Childhood and Adult Tumors.** UCSF at Childrens Hospital, San Francisco. Saturday.

March 12—**Obstetrics and Gynecology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

March 12-13—**Neuropsychiatry in Daily Practice.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

March 13-17—**Alumni Postgraduate Convention, LLU.** Mar. 13-14 (Sunday-Monday)—Refresher Courses. White Memorial Medical Center. Mar. 15-17 (Tuesday-Thursday)—Scientific Assembly. Ambassador Hotel, Los Angeles. Contact: Samuel H. Fritz, M.D., general chairman, 1832 E. Michigan Avenue, Los Angeles 90033.

March 16—**Symposium on Obesity.** USC. Wednesday.

March 19—**Rheumatic Diseases.** Pres. Med. Ctr. Saturday. 8 hours. $30.

March 19-20—**California Radiological Society Annual Meeting.** Biltmore Hotel, Los Angeles. Saturday-Sunday. Contact: L. H. Garland, M.D., 450 Sutter Street, San Francisco.

March 20-23—**CALIFORNIA MEDICAL ASSOCIATION 94th Annual Session.** Scientific theme: "CURRENT CONCEPTS IN THERAPY: Coronary Artery Disease. Gastrointestinal Hemorrhage. Renal Failure." Biltmore Hotel, Los Angeles. Sunday-Wednesday. Contact: Mr. John Hunton, executive secretary, 693 Sutter Street, San Francisco 94102.

March 25-27—**Sex Disorders in Clinical Practice.** UCSF. Friday-Sunday.

March 26—**Endocrinology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

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The Physician's BOOKSHELF

CURRENT PRACTICE IN ORTHOPAEDIC SURGERY, 1964—Volume 2—John P. Adams, B.S., M.D., F.A.C.S., Professor of Orthopedic Surgery and Chairman of Orthopedic Section, The George Washington University School of Medicine and Hospital, Washington, D.C., Editor. The C. V. Mosby Company, Saint Louis, 1964. 231 pages, $13.50.

The book consists of some nine chapters, each written by a different author. Chapter I is entitled "Tendon Transfers for Nerve Paralysis of the Hand and Wrist." This chapter is a summary of the various accepted and workable tendon transfers for nerve paralysis of the hand and wrist. The diagrammatic illustrations are particularly valuable for quick appraisal and the text is equally straight-forward and understandable. One tendon muscle unit for transfer purposes deserves more attention, perhaps, namely the brachial radialis which is readily available to go either dorsally or volarward.

The chapter on "Sensibility of the Hand" is an excellent review of what is known to date about sensation and its loss and recovery in respect to the hand. Everyone dealing with the sensory aspect of the hand should be fully cognizant of this information. Recent interest in the problem has been spear-headed by Swedish investigators with the result that old methods of evaluation are being discarded and new methods of nerve suture instituted. All undoubtedly will lead to improvement in the results of nerve suture which is sorely needed.

Within the confines of twenty-two short pages, Mr. Holdsworth covers the subject of fractures and dislocations of the thoracic and lumbar spine with and without neurological involvement. The types of injury, their mechanisms of production and the precise way the cauda equina, nerve roots and spinal cords are involved, are concisely explained and illustrated by photograph and diagram. The fundamentals of treatment, not only for the broken and displaced vertebrae, but also for the neurological complications are succinctly enumerated. This chapter is a veritable gem of brevity and clarity. The author is obviously a master of his subject.

Chapter IV—"Management of Acute Vascular Injuries of the Extremities"—The authors with considerable experience in this field present the basic concepts of diagnosis, prognosis and treatment in an authoritative manner. This contribution is valuable to the orthopedic surgeon, the vascular surgeon and general surgeon who treats traumatic injuries. A lack of precise sentence structure and careful proof reading detract only slightly from the generally sound presentation.

Chapter VI is devoted to the "Treatment of Injuries of Proximal Interphalangeal Joints of Fingers." Most of the common injuries creating stiffness of the proximal interphalangeal joints are considered, and one of these for each is outlined. For the stiffened proximal interphalangeal joints without local trauma, active use of the joint to promote its mobilization is emphasized. There are no long series with tabulated results, and while the surgeon can and must help in a mechanical way at times, it is quite evident that the problem is still with us, and for the most part the passage of time with active use still hands the most promise of functional recovery in the vast majority of cases.

Although the chapter on "Fractures of the Elbow in Children" covers all of those commonly seen, the reviewer was particularly impressed by their recommendation for the treatment of supracondylar fracture which, of course, is the common one that all general and orthopedic surgeons are called upon to treat. They have had very great success with and describe the most conservative Dunlop skin traction. This method has worked very satisfactorily for them. It is very clearly and accurately described and should be known to every orthopedic surgeon.

There is another chapter on "Fractures of the Humeral Shaft" in which a strong case for the light weight hanging cast in the treatment of fractures of the shaft of the humerus and particularly for the nonoperative treatment of these fractures is made. In this chapter ten rules which must be scrupiously observed are enunciated. These can be easily followed by the average doctor. Over 90 per cent success has followed. In addition, he discloses the rare indications for open reduction, lists the devices he recommends or condemns, lays down six important rules for after care and rehabilitation. Finally, there are three short paragraphs on the handling of the rare case of non-union.

Chapter VIII takes up the subject of some psychological characteristics associated with orthopedic complaints. Studies on several groups of orthopedic patients by using the Minnesota Multiphasic Personality Inventory were made. Although the study is of some interest, no very satisfactory information which one could employ in the daily handling of patients was brought out in this particular report.

The final chapter is entitled "Comparative Biology of Mineral Deposition." Here again, although no concrete facts are forthcoming which would help a surgeon in his daily care of fractures, nevertheless, this reviewer found this particular chapter of very great interest. The central theme of the chapter is that mineral deposition in all animals from the most primitive, to vertebrates laying down bones and teeth follows the same broad general biological pattern of mineral deposition onto an organic matrix. The environmental factors assisting in or governing the deposition of calcium in clams, lobsters, crabs, crayfish, shrimps and so forth, is all described in addition to the known facts about calcium deposition in the more primitive forms such as the protozoa and other forms with calcareous skeletons living in the plankton of the sea water.

Considering the book as a whole, it can be said that a wide variety of subjects is covered. Each chapter is obviously written by an expert in a very readily understood language and copiously accompanied by excellent illustrations. It is quite apparent that this second volume of *Current Practice of Orthopedic Surgery* will have a very great appeal for general practitioners, general surgeons, as well as orthopedic surgeons, and it is highly recommended.

BACTERIAL AND MYCOTIC INFECTIONS OF MAN —Fourth Edition—Edited by René J. Dubos, Ph.D., and James G. Hirsch, M.D., Professors, The Rockefeller Institute. J. B. Lippincott Company, Philadelphia and Montreal, 1965. 1025 pages, $14.50.

Since 1948 when "Bacterial and Mycotic Infections of Man" first appeared, that book and its companion volume "Viral and Rickettsial Infections of Man" have been widely respected texts and sources of reference. Edited by members of the Rockefeller Institute and written by distinguished investigators, these books were models of thoughtful and deliberate presentation of all fundamental aspects of microbiology. However, the increasingly long gaps between editions (4, 6 and 7 years respectively) somewhat detracted from the practical usefulness of these books in a very rapidly moving field.

The present, fourth, edition is refreshingly original and beautifully presented. With James G. Hirsch's imaginative editorship added to the traditional one of René J. Dubos, only a minority of individual chapters are "rewrite" jobs. Many chapters are entirely new in concept and presentation. Each chapter provides competent coverage of a topic, often with considerable breadth and sophistication, and a good bibliography.

While a reviewer might quarrel with a few isolated features, there can be little doubt that this 4th edition gives a balanced and updated view of all the most important aspects of microbial structure, function, and pathogenesis, and of host responses which determine resistance or hypersensitivity. For many physicians, teachers and students this book will be a welcome source of reliable reference. In the crowded curriculum of medical students the 960 pages will be read from cover to cover by only a few dedicated and diligent individuals. All, however, will cherish the volume as a good place to look up information in some depth and to find thoughtful points of view. Excellent illustrations and a comprehensive index add to the usefulness of the volume. The price is surprisingly modest ($14.50).

ERNEST JAWETZ, M.D.

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CLINICAL TESTING OF NEW DRUGS—Edited by Arthur D. Herrick and McKeen Cattell. Revere Publishing Company, Inc., New York, N.Y., 1965. 362 pages, $11.75.

This is a timely and helpful book, edited by men of wisdom and experience, and with contributions by outstanding scientists, clinicians, and government officials. The volume is a relatively sophisticated approach to the old problem of how to judge clinically whether or not new drugs are "safe and efficacious" for ordinary use by physicians. With the wide variation in human individuality now evident, it is becoming clear that no drug is fully safe for all persons, nor fully effective in all patients. To agree on what is reasonable safety and effectiveness in drugs is becoming increasingly difficult.

The editors of the volume are men of experience: Arthur Herrick has long been a consultant in New York for drug research, and founded *The Journal of New Drugs,* while McKeen Cattell is Professor Emeritus of Pharmacology at Cornell Medical College, New York, and editor of *The Journal of New Drugs*. While Herrick notes that medicine seldom flourishes in a bureaucratic atmosphere, the appendices to the text give full opportunity to members of the Food and Drug Administration to explain their responsibilities and programs. Frances O. Kelsey reviews the objectives and functions of the Investigational Drug Branch, as well as problems involved; Earl Meyers describes the role of the Food and Drug Administration in the testing of new drugs, and George P. Larrick tells how the Food and Drug Administration evaluates new drug applications.

The main part of the book consists of four parts: preclinical testing, the clinical investigator, clinical trials, and evaluation of results. In the part on preclinical testing, Eldon Boyd and G. E. Paget discuss toxicity studies; Leon Goldberg considers the predictive value of animal studies, and Joseph Jerome describes the selection of public names. In considering the clinical investigators, Arthur Herrick notes their responsibilities, while Theodore Greiner gives an excellent discussion on the ethics of drug research on humans. Under clinical trials, Dale Friend discusses evaluation, Marvin Schneiderman considers controls and size, our Henry Garland notes variations in laboratory and clinical observers, Daniel Green reflects on clinical proof of safety and effectiveness in proprietary medications, and Donald Mainland details the development of multiclinic trials. In the section on evaluation of results, John Marks and D. J. Finney consider "placebomania," Jonathan Cole reports on judging drug treatment in psychiatry, and Seymour Fisher with R. E. A. Mapes criticize conventional statistical procedures used in drug testing.

The scope of the volume indicates the great progress which has been made in the past half-century in the careful clinical evaluation of new drugs. While many of the principles were outlined long ago, the current methods of drug testing are now so well controlled that physicians can be assured of relative safety and effectiveness of new drugs through the cooperation of the drug industry, academic pharmacology, and the Food and Drug Administration.

CHAUNCEY D. LEAKE, M.D.

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PREVENTIVE MEDICINE—Principles of Prevention in the Occurrence and Progression of Disease—Second Edition—Edited by Herman E. Hilleboe, M.D., Professor of Public Health Practice, Columbia University, School of Public Health and Administrative Medicine; and Granville W. Larimore, M.D., First Deputy Commissioner of Health, State of New York, Department of Health, Albany. W. B. Saunders Company, Philadelphia and London, 1965. 523 pages, $12.00.

In many respects the second edition of this text resembles the first, published in 1959. Thus, much of the complimentary review of that edition, which appeared in CALIFORNIA MEDICINE, September 1959, page 178, is still valid.

This second edition is somewhat shorter than the first, for the number of pages has been reduced from 731 to 523, and the number of figures from 59 to 49. At the same time, the number of contributors has increased from 31 to 35, of whom 23 participated in both editions. As before, the majority of contributors are recognized experts in their respective specialties, and most of them are identified with the New York State Health Department. Nevertheless, their points of view are not provincial, but are equally pertinent to California and New York.

As in the earlier edition, the text is divided into three major subdivisions. The first embraces the "Prevention of Occurrence (of Disease)" and deals primarily with the fields of environmental sanitation, prophylaxis including immunization against selected diseases, and nutrition. These conform to the traditional concepts of "preventive medicine" and, in addition, includes certain aspects of "public health."

"Prevention of Progression (of Disease)" is considered in the second major subdivision of this text. Here the early detection of selected diseases by periodic health surveys is emphasized. The sections entitled "Rehabilitation," "Alcoholism," and "Narcotic Addiction," deal with many aspects of these problems including the prevention of occurrence as well as the prevention of progression. Indeed, these dual aspects of many of the specific health problems mentioned throughout the text are inseparable, and the attempt by the authors to divide them into distinct sections is somewhat arbitrary.

In the third major subdivision, "Supporting Services for Preventive Medicine," the authors discuss an interesting combination of techniques, professions and health agencies. Included are such titles as "Health Education and the Social Sciences," "Public Health Nursing," "Vital Statistics," "Epidemiologic Methods and Inferences," "Voluntary Health Agencies," and "Official Health Agencies." These are subjects traditionally considered as a part of "public health." Additional topics, such as "Continuing Education for Physicians," and "Social Work" would seem as appropriate in any other medical textbook as in this one.

Most of the information contained in this book is of general interest and presented at a level readily understood by well-educated lay persons. It should also be quite profitable for beginning medical students and for those in the ancillary health sciences, but seems to be of limited value to professionals in the field. Each section is followed by a list of pertinent references, many of which are recent. The value of the book would be increased, however, if a greater proportion of the references were updated.

William W. Stiles, M.D.

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PROGRESS IN HEMATOLOGY—Volume IV—Edited by Carl V. Moore, M.D., and Elmer B. Brown, M.D.; with 21 contributors. Grune & Stratton, Inc., New York and London, 1964. 309 pages, $13.75.

This publication has been undertaken by new editors and does not suffer from being "spotty" as in previous volumes. Ten papers are included and cover the subjects of Heme Synthesis, Methemoglobinemia, Erythropoietin, Chemistry of ABH Group Substances, Lead Poisoning, Chloramphenicol Toxicity, Myeloma Proteins and Macroglobulinemia, Acute Leukemia, Von Willebrand's Disease, Platelet and Leukocyte Isoantigens and Antibodies. The material is consistently on the highest scientific level but with a clinical orientation one expects from these editors. With the field of hematology not being systematically reviewed in any journal, conference, seminar or annual publication, it is hoped that this volume will appear, even annually, with periodic up-to-date reviews of progress in each area of hematology. Volume IV is a good start and will be of value to all, investigator, laboratory worker and clinician, interested in the field of hematology.

William F. Luttgens, M.D.

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MOTOR FUNCTION IN THE LOWER EXTREMITY—Analyses by Electronic Instrumentation—J. R. Close, M.D., Department of Orthopaedic Surgery, Highland-Alameda County Hospital, Oakland, Calif.; and Department of Orthopaedic Surgery, University of California School of Medicine, San Francisco, Calif. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1963. 156 pages, $10.75.

This reviewer has been indeed impressed at the useful collation in this book of much scattered research material on movement patterns in the lower extremity. It undoubtedly contains some of the finest references to the author's previously reported findings on phasic activity in translocated tendons. This portion of the monograph can easily be recommended for orthopedic surgeons, and others concerned with this particular branch of clinical practice.

However, there exists great doubt in this reviewer's mind that the description of the book on the fly-leaf is an accurate one, as it indicates a wider field of interest than the actual contents would indicate. So much of the book is taken up with the description of electronic methodology that it can scarcely be described aptly as being of interest to the average "orthopedist, physiatrist, neurologist or physical therapist." The numerous chapters on instrumentation will undoubtedly have interest to the technically-inclined physician, but will be largely beyond the comprehension of the average clinician in any one of these fields. It is recommended therefore for study by a select few, who have advanced training in electronic methods of monitoring clinical events. It is also highly doubtful that the advanced methods of telemetry, described in this monograph, will have either current, or early, prospect of application to these clinical events, in the hands of the physicians described on the fly-leaf.

Another criticism of this monograph, which this reviewer has heard voiced rather widely, is that it is indifferently organized and somewhat misleadingly titled. There is a regrettable lack of correspondence between excellent drawings and the textual material they allude to. The reader frequently finds himself jumping from page to page to find a particular illustration, which may be as much as four pages removed from the text. In summary, this book is highly recommended to the clinician with a broad laboratory background in electronic recording of either normal or abnormal function.

Walter J. Treanor, M.D.

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FREEDOM TO EXPERIENCE—A Study of Psychological Change from a Psychoanalytic Point of View—Benjamin Wolstein, Ph.D., Faculty, W. A. White Institute of Psychiatry, Psychoanalysis and Psychology; Clinical Professor of Psychology, Adelphi University. Grune & Stratton, Inc., New York and London, 1965. 292 pages, $8.50.

It will surely be a great day for psychiatry when authors no longer fight with nor appeal for support to Freud, but rather concern themselves with psychoanalytic theory and practice as they are today. This continued engagement with the views of Freud is becoming ludicrous; what would we think of bacteriologists who still embroiled themselves with Pasteur or Ehrlich? Unfortunately, this history is still very much alive for Dr. Wolstein, somewhat as the issues of the Civil War are still alive in the South, unchanged by time. He takes a great deal of space detailing the views of Freud on such matters as resistance, regression, transference and countertransference. After this, he makes a very few passing references to later authors whose work he then ignores along with a great body of material not even referred to, although it bears strongly on what is being discussed. The effect of this is to set up a straw man, purported to represent the "classical" psychoanalytic view as it is today, which he then proceeds to attack. For example, he takes issue with the concept of resistance as something to be overcome, as on the field of battle, to allow the analyst to get at the id, his presumed goal. Well and good, but this ancient view of resistance would find no adherents either among the most orthodox of analysts today, for whom the analysis of resistance is the cornerstone of treatment. Or, as a second example, he deplores the idea of the analyst as a mirror, but this view of the analyst has been tremendously modified during the development of psychoanalytic technique even in the most orthodox circles. This sort of arguing with the past obscures Dr. Wolstein's real differences with orthodox psychoanalytic theory and practice, which is unfortunate, as he raises some interesting points. It is regrettable that these points are also further obscured by his repetitiousness, murky prose and bizarre punctuation; one wonders where the editor was. Dr. Wolstein discusses certain aspects of the topics of resistance, regression, transference, countertransference and the shared experience of analyst and patient. The main point would seem to be that the countertransference reactions of the analyst should receive far more attention by analyst and patient than is customary, to the end that their shared, unique experience can be focused upon. He also stresses the importance of attention to and support of the developmental capacities of the patient. It would have helped understanding if Dr. Wolstein had provided more clinical examples so that it would be possible to see just what the important differences in practice are as compared to more orthodox psychoanalysis. This book is definitely not suitable for the general medical reader, not only because of the distortions noted above, but also because understanding it requires a good deal of background in the psychoanalytic literature.

ADRIENNE APPLEGARTH, M.D.

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BRAIN FUNCTION—Proceedings of the First Conference, 1961—Cortical Excitability and Steady Potentials, Relations of Basic Research to Space Biology. Sponsored by the Brain Research Institute, University of California, Los Angeles, in collaboration with the American Institute of Biological Sciences and with the support of the U.S. Air Force Systems Command. Mary A. B. Brazier, Editor. UCLA Forum in Medical Sciences: Number 1. University of California Press, Berkeley and Los Angeles, 1963. (Publication date—1964) 390 pages, $10.00.

The terms of reference for this conference was to explore the knowledge and meaning of steady potential changes, which can be recorded between the cortical surface and indifferent structures. Recent study has led to the consideration that this electrical sign may be an important indicator of cortical excitability. The meaning of negative or positive shifts in terms of underlying mechanisms, such as ion transport, transmitter substances, membrane changes along with microstructure and microchemistry of the brain was explored.

These were the basic considerations, but the prime reason for having the conference was the recognition of a need to understand how man's brain will be affected by the stresses of air space life, and to this end attention was focused on the Steady Potentials. The position of the significance of Steady Potentials may be best presented in the words of Dr. Purpura, who in his excellent paper, "Review and Critique," stated, "For despite claims that the measurement of cortical steady potentials may provide important information on the functional activity of the brain, one cannot help but wonder precisely what kind of information is imparted by the data."

The Proceedings do afford a readily accessible means of seeing the interests of the foremost workers in this particular field. However, it is a field of considerable restriction at the present time and of interest only to a small number of neurophysiologists. It is unlikely that this book will be of interest to more than a certain number of neurophysiologists, neurochemists, and neurological physicians interested in neurophysiology.

DONALD MACRAE, M.D.

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CIBA FOUNDATION STUDY GROUP NO. 18—Brain-Thyroid Relationships with Special Reference to Thyroid Disorders. Edited by Margaret P. Cameron, M.A., and Maeve O'Connor, B.A. In honour of Professor S. Artunkal. Little, Brown and Company, Boston, Mass., 1964. 117 pages, $1.95.

The reading of the proceedings of a study group in which the recent advances in the subject to be discussed are presented in summarized, followed by individual papers and by long question and answer periods (questions to which at present there are no answers, though they reveal the directions of thoughts concerning these questions) is a delightful exercise and also an excellent introduction to current thinking, recent research, and projected efforts. This little collection fits beautifully into such a background. It is excellent and brings one up to the present in the research activities on brain-thyroid relationships which are pertinent.

The subsequent papers in themselves do not attempt to present a comprehensive account of brain-thyroid relationships, but rather deal with specific aspects, such as the function of the hypothalamus in regulation of pituitary-thyroid activity, hypothalamic temperature and thyroid activity, effect of thyroid hormones on brain differentiation, longitudinal study of intelligence quotient in treated congenital hypothyroidism, and psychological studies in hyperthyroidism. This small book, containing the Proceedings of Study Group No. 18 will not only be of interest to endocrinologists, neurologists, and psychiatrists, but also to the whole discipline of medicine. I would also consider this a very useful piece of reading material for students who have the interest to read further along these lines.

DONALD MACRAE, M.D.

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PROGRESS IN RADIATION THERAPY—Volume III— Edited by Franz Buschke, M.D., Professor of Radiology, University of California School of Medicine; Chief of the Section of Therapeutic Radiology, University of California Hospitals, San Francisco, California. Grune & Stratton, Inc., New York, 1965. 242 pages, $14.50.

This small monograph by 15 contributors summarizes certain aspects of radiotherapy in recent years.

The general tone of the monograph is set by the article "Present status of combined radiation therapy and chemotherapy" by Kligerman, who stresses that "Throughout the current review, the most glaring deficiency was failure to have control patients." He reports previously unpublished investigations leading to the conclusion that his group was unable to find any evidence of increased effectiveness of radiation when 5 FU is added simultaneously. Similarly, he cites studies showing that the case for therapeutic synergism for actinomycin D has not been made. He feels that at the present time no proven drug exists by which radiation may be augmented.

Vaeth reports a series of patients who developed radiation myelitis following the use of megavoltage therapy in the neck and upper mediastinum.

Dalley (of the Royal Marsden Hospital) discusses radiotherapy in malignant tumors of the temporal bone and observes that "Kilocurie telecobalt units and linear accelerators are potentially dangerous apparatus because of their large depth dose, and the proximity of both orbits and the brain to the tumor region."

Lenz summarizes a long experience with radiotherapy of mammary cancer, reports long-term results obtained with orthovoltage, and notes that survival was the same as that obtained in a subsequent megavoltage series. He cites the one beautifully controlled study of Kaae and Johansen of Denmark which showed that simple mastectomy plus radical postoperative radiotherapy yields the same survival rate as extended radical mastectomy, with a slightly lower local recurrence rate. (The equally beautiful controlled study of orthovoltage and megavoltage in the treatment of cancer of the cervix published by Paterson of Manchester last year is not noted in this monograph—a rather curious omission. This study showed that the three-year cure rate in Stage II cancer of the cervix was significantly better with orthovoltage than with megavoltage.)

The chapter on "Radiation therapy in childhood" by Darte of Canada is up-to-date and informative. This author recommends conventional therapy (orthovoltage) for most patients with Wilms' Tumors, combined as a rule with appropriate abdominal surgery. He also uses radiation of the same energy range for retinoblastoma.

The full flowering of Parkinson's Law is illustrated in the staff requirements recommended by Kaplan for clinical investigative programs in radiotherapy. This author also fails to mention the notable examples completed and the standards set by the Manchester group. Finally, there are useful chapters on statistical evaluation of the results of treatment of cancer by Phillips and on education of medical students by Kramer. One senses the unexpressed conclusion that radiation therapy should be taught to medical students much as surgical therapy is taught . . . along with and as a part of the general training program and not as a separate exercise in oncology alone. Indeed, the observations endorse the report of the Council on Medical Education (J.A.M.A., 192:142, May 10, 1965) that "The great need in this country is still for the physician trained in all aspects of the specialty of radiology." Most parts of the country neither need nor can support a separate radiation therapist. The results in most forms of treatable human cancer are as good if not better in the hands of the general radiologist as compared to the results obtained by the physician limiting his practice exclusively to radiation therapy of cancer.

L. Henry Garland, M.D.

* * *

BRAIN TUMORS—Their Biology and Pathology—Second American Edition, based on the Fourth German Edition—K. J. Zulch, M.D., Professor of Neurology, University of Cologne, and Head, Department of General Neurology, Max Planck Institute for Brain Research. Translated by Alan B. Rothballer, M.D., M.Sc., Associate Professor of Neurological Surgery and of Anatomy, Albert Einstein College of Medicine, and Visiting Neurosurgeon, Bronx Municipal Hospital Center, New York, N.Y.; and Jerzy Olszewski, M.D., Ph.D., Professor of Neuropathology, University of Toronto, Toronto, Canada. Springer Publishing Company, Inc., New York, 1965. 326 pages, $11.00.

Eight years have elapsed between the first and the second American edition of this most useful book. The author has deleted nothing from the first edition but has added sections to bring it up to date in terms of the contributions that have been made on the subject since 1957.

The additions deserve comment:

The International Union against Cancer classification is reproduced and the author offers a scale of increasing malignancy of the maor types of intracranial tumor. The section on the genesis of experimental tumors is expanded, especially as it concerns the gliomas and the concept of immune responses against transplanted tumors. The significance of hereditary factors is recognized in a modest expansion of that section. The subdivision on "Accident and Brain Tumors" has been appropriately renamed "Trauma and Brain Tumors." The new data on the spontaneous occurrence of brain tumors in animals is included in an addition to that subdivision and a brief concluding comment is added to the chapter on the pathogenesis of brain tumors.

Among the additions to the statistical data is a section on the epidemiology of brain tumors in man. The chapter dealing with the gross and microscopic appearance adds paragraphs dealing with the histochemistry of tumor and the short section on tissue culture contains a welcome supplementation. A section on delayed radiation necrosis of the brain is timely, and a new section on electron-microscopy of brain tumors is included although this is not as extensive as it might have been. In the interest of maintaining the size of the volume very close to that of the original edition, this brevity may be excused. The section on brain edema is also expanded briefly, but this complex problem cannot be dealt with in depth and the balanced emphasis in the volume be retained.

Certain histologic diagnostic refinements are offered from which the astroblastoma category has been discarded. Recent data have also been added to the chapter on the origin of the Schwann cells. Another expanded section is that pertaining to the reticulum cell sarcoma.

It is regrettable that some of the most recent monographs cannot have been included in the expanded series of references. Also the recent information on identification of pituitary cell types using newer histologic techniques has not been covered. A supplemental bibliography has been added as a second part to the references cited in the first edition and includes those occurring in the years between editions.

In general, this book remains the most useful survey of brain tumors. It should be on the shelf of everyone dealing with clinical neurological problems. It is a "must" for those in training in the clinical neurological sciences and it is a ready reference to the neuropathologist, the neurosurgeon and the neurologist. It has value in providing an understanding to the other practitioners of medicine and perpetuates the value of the first edition. The second edition represents a brief supplementation in strategic areas without any deletions from the first.

W. Eugene Stern, M.D.

* * *

SYNOPSIS OF CONTEMPORARY PSYCHIATRY—Third Edition—George A. Ulett, B.A., M.S., M.D., Ph.D., Professor and Chairman, Department of Psychiatry at the Missouri Institute of Psychiatry (St. Louis), University of Missouri School of Medicine; Director, Division of Mental Diseases for the State of Missouri; and D. Wells Goodrich, M.D., Chief, Child Research Branch, National Institute of Mental Health, United States Public Health Service, Bethesda, Md. The C. V. Mosby Company, Saint Louis, 1965. 299 pages, $6.75.

This little handbook is designed as a brief psychiatric text to serve as a quick reference for residents, interns, medical students, nurses and general practitioners. It is small, concisely written and color tagged into three sections—history taking and diagnostic procedures, clinical syndromes and therapeutic measures. It fulfills its stated purpose in an eclectic manner. The authors mention that the book has been criticized by some reviewers as "too organic" and by others as "too psychoanalytic." This reviewer would tend to agree with the view that it leans in the organic direction.

* * *

SURGERY OF THE BILIARY PASSAGES AND THE PANCREAS—Walter Hess, Privatdozent Dr. med., Zurich; Dozent of Surgery, Faculty of Medicine, University of Basle, Switzerland; formerly Professor of Surgery, Medical School, University of Alexandria, Egypt. Translated from the German by Heinrich Lamm, Dr. med., F.A.C.S., Harlingen, Texas. Operative Drawings by Ingrid Schaumburg. D. Van Nostrand Company, Inc., Princeton, New Jersey, 1965. 638 pages, $25.00.

In this volume, surgery of the biliary-pancreatic system is subjected to an encyclopedic review. The author's personal experience with 1,654 "biliary patients" in his European practice, his extensive research in this field, and his early interest in radiomamometry give him claim to a certain degree of authority on this subject.

The first part of the book is devoted to an extensive review of normal anatomy and its variations, and to normal and pathological physiology. In addition a long chapter is devoted to the refined intra-operative diagnostic techniques of cholangiography, pancreatography, choledochoscopy, and radiomamometry. Throughout these basic discussions there are numerous references to clinical situations.

A comprehensive presentation of operative techniques begins the second part of the book. This is followed by a detailed "when and what to do" section. Pre-operative care, anesthesia, and post-operative care are described in later chapters. The volume concludes with a discussion of general and individual post-operative complaints and their management.

An extensive bibliography follows each chapter and the index is complete and well detailed. An outstanding feature of the book are its illustrations. The anatomical and surgical drawings are excellent, and along with the fine X-ray reproductions add immeasurable value to the volume.

It must be assumed that the tedious task of translation from the original German was done faithfully. Despite the consistent use of American terms for instruments and drugs, a great deal of the terminology and phraseology has a definite European flavor. The general presentation of the material and the layout of the text will appear rather unusual to the average reader of American surgical texts. Once this difference in readability is resolved, all surgeons interested in the fascinating problems of diagnosis and management of biliopancreatic pathology will find this a most useful complete reference volume with a Continental touch.

David Sachs, M.D.

* * *

RHEUMATIC FEVER—Diagnosis, Management and Prevention—Milton Markowitz, A.B., M.D., Assistant Pediatrician-in-Chief, Sinai Hospital of Baltimore; Associate Professor of Pediatrics, Johns Hopkins University School of Medicine; Pediatrician-in-Charge, Rheumatic Fever Clinic, Harriet Lane Home Service, Children's Medical and Surgical Center, The Johns Hopkins Hospital; and Ann Gayler Kuttner, B.S., Ph.D., M.D., Associate Professor of Pediatrics, Emeritus, New York University, Bellevue Medical Center; Visiting Scientist, Streptococcal Disease Laboratory, Sinai Hospital of Baltimore. With a special chapter on Community Health Services by Leon Gordis, A.B., M.D., Field Officer, Heart Disease Control Program, U.S. Public Health Service; Fellow in Pediatrics, Sinai Hospital and The Johns Hopkins Hospital. This is Volume II in the Series: Major Problems in Clinical Pediatrics—Alexander J. Schaffer, Consulting Editor. W. B. Saunders Company, Philadelphia and London, 1965. 242 pages, $7.50.

This is the second volume of a series of publications by W. B. Saunders Company entitled, "Major Problems in Clinical Pediatrics." This treatise on rheumatic fever maintains the high level of quality set by its predecessor, Mary Ellen Avery's "The Lung and its Disorders in the Newborn Infant." Ann Kuttner, a physician and microbiologist, has had a lifetime of experience with rheumatic fever and the streptococcus—both at the bedside and in the laboratory. Her co-author, Dr. Milton Markowitz, heads the rheumatic fever program for children at Johns Hopkins Hospital. Between them, they have produced an authoritative, very much up to date and readable monograph.

They start with a discussion of the changing pattern of rheumatic fever, followed by chapters on the biology of the streptococcus and the etiology and pathogenesis of rheumatic fever. Several chapters are devoted to the clinical and laboratory manifestations of the disease, as well as pitfalls of differential diagnosis. The section on therapy gives a clear presentation of the evidence provided by the several studies which compare aspirin and steroids, as well as the authors' personal recommendations. The subect of chronic rheumatic heart disease and its complications is covered briefly but very adequately. The final chapter by Leon Gordis, entitled, "Community Health Services," deals with the public health aspects of rheumatic fever control and prevention, and includes a number of official statements and recommendations by various health agencies. Some 500 well selected and current references are provided in the bibliography.

With the decreased incidence of rheumatic fever many physicians do not see this disease often enough to maintain a high level of competence in this area. This excellent volume is recommended to practicing physicians, house officers, and medical students as a valuable refresher in this area of medicine.

Moses Grossman, M.D.

* * *

Tracy's THE DOCTOR AS A WITNESS—Second Edition—William J. Curran: LL.M., S.M. Hyg., Edward R. Utley Professor of Legal Medicine and Director, Law-Medicine Institute, Boston University. W. B. Saunders Company, Philadelphia, 1965. 196 pages, $5.75.

In our litigious State this new edition will be dull but necessary reading for many physicians. There are 11 chapters, ranging from the elementary to the highly technical in matters forensic. The fact that trial law is a matter of emotion-manipulation and fact-obfuscation is not concealed.

There is advice for the different types of specialist before and on the witness stand. There is discussion of evaluation of disability in other than Workmen's Compensation cases.

The author goes into the use of various devices such as slides, movies, roentgenograms and so forth in the courtroom. He does not mention the late and admirable San Mateo County Judge who refused to allow any roentgenograms in court. The latter observed that the average juryman was not competent to interpret them and that he would be much better informed to read or listen to the radiologist's report.

Each of the chapters contains a list of recommended reading and references. These alone will probably repay many physicians the modest cost of this convenient volume.

L. Henry Garland, M.D.

* * *

THE PEDIATRIC PATIENT 1965—Sarah R. Gustafson, Ph.D., Director, Department of Medical Literature, Hoffman-La Roche Inc., Nutley, New Jersey, Coordinating Editor; and David Baird Coursin, M.D., F.A.A.P., Director of Research, Research Institute, St. Joseph's Hospital, Lancaster, Pennsylvania, Consulting Editor. J. B. Lippincott Company, Philadelphia, 1965. 216 pages, $6.00.

This is the third of what is becoming established as an annual volume prepared by Drs. Sarah Gustafson and David Coursin. In addition to being sold, these books are widely distributed among physicians by the sales representatives of Hoffmann-La Roche. The topics selected are of current interest and different from those covered in the previous two years. The references are generally up to and including the 1963 literature with a few 1964 references. The chapters are very well done particularly considering that each was not written by an expert in the field.

The opening section is "The New Immunology." This is a good review of the modern concept of immunology with a clinical section on autoimmune diseases. Other chapters include allergy, the newborn, hormonal disorders, vision, adolescence and new syndromes.

This little book can be perused rapidly and will provide the busy practitioner who has not been able to read his pediatric journals as much as he might have liked with a bird's-eye view of the new concepts and developments in the areas covered here.

Moses Grossman, M.D.

CURRENT PSYCHIATRIC THERAPIES—Vol. V—1965, with Cumulative Index to Vols. I-V—An Annual Publication, edited by Jules H. Masserman, M.D., Professor and Co-chairman of Psychiatry, Northwestern University, Chicago, Illinois. Grune & Stratton, Inc., New York, 1965. 306 pages, $10.75.

This volume is the first of a series that, every five years, will review progress in psychiatric therapy. An introductory review of the present and future of psychiatry by Dr. Howard Rome, is followed by nine sections—four papers on "History and Rationale"; four on "Childhood and Adolescence"; eleven on "Individual Psychotherapy"; three on "Group Therapy"; three on "The Family"; three on "Community Psychiatry"; four on "Institutional Psychiatry"; four on "Rehabilitation"; and two on "Transcultural Psychiatry."

It is inevitable that the papers in a compendium of this sort will vary in quality but the reader is likely to find something that will be of interest to his particular taste and the book does fulfill a useful purpose as a "once over lightly" on a wide variety of current subjects. There is one curious, striking omission—neuropsychopharmacology. The only paper on drug therapy as such is in the section on Individual Psychotherapy—"Techniques of starting the psychotherapy patient on psychiatric drugs" by Bernard Wilkens and Sidney Malitz.

He who wishes to read about advances in drug therapy of psychiatric disorders should read elsewhere. Otherwise recommended as an integrated series of short, review papers.

* * *

PRACTITIONER'S ILLUSTRATED DERMATOLOGY—Howard T. Behrman, M.D., Professor of Clinical Dermatology and Director of Dermatologic Research, New York Medical College; with the collaboration of Theodore A. Labow, M.D., Assistant in Dermatology, Vanderbilt Clinic, Columbia-Presbyterian Medical Center. Grune & Stratton, Inc., New York, 1965. 189 pages, $9.75.

It is a pleasure to review a new book in which the goals and objectives which the authors set for themselves were achieved. In the preface of the Practitioner's Illustrated Dermatology, the authors Behrman and Labow state "It is to be emphasized that this primer is for the student and the physician with limited access to a consultant and not for the dermatologist. The text has been limited to those skin diseases most commonly seen in practice and some of the omissions have been arbitrary." They have accomplished this goal in what I consider to be a superior manner. Terminatology has been greatly simplified, and on the opposite pages to each disease or group of diseases there are color photographs illustrating typical examples. There are well over 200 color photographs in this volume and no black and white illustrations at all. The photographs have been well selected, illustrating usual manifestations rather than rare examples.

On the page opposite the photographs the diseases themselves are well presented in a simplified manner, with a brief summary of what the disease is, what it is caused by, clinical features and treatment. Almost all of the considerable detail required by the specialist and often so confusing to the generalist has been completely omitted. Treatment has been handled in the same fashion.

In the last 30 pages of the book there is presented a formulary which includes a discussion of external applications and internal medications. Here again simplified terminatology and presentation has been utilized to great advantage.

It is my opinion that for the medical student, house staff and general physician this volume will prove extremely valuable. The student or house staff may use it primarily to gain an overall broad knowledge of the field of dermatology and the general physician will, I believe, find it a great help in his daily practice.

This book will not serve the intern or resident who desires depth in his study nor will it serve the dermatologist. However, the authors carefully point out that the volume was not intended for these groups.

Thomas H. Sternberg, M.D.

* * *

FUNDAMENTALS OF ORTHOPAEDICS—John J. Gartland, A.B., M.D., Assistant Professor of Orthopaedic Surgery, Jefferson Medical College. W. B. Saunders Company, Philadelphia and London, 1965. 338 pages, $8.00.

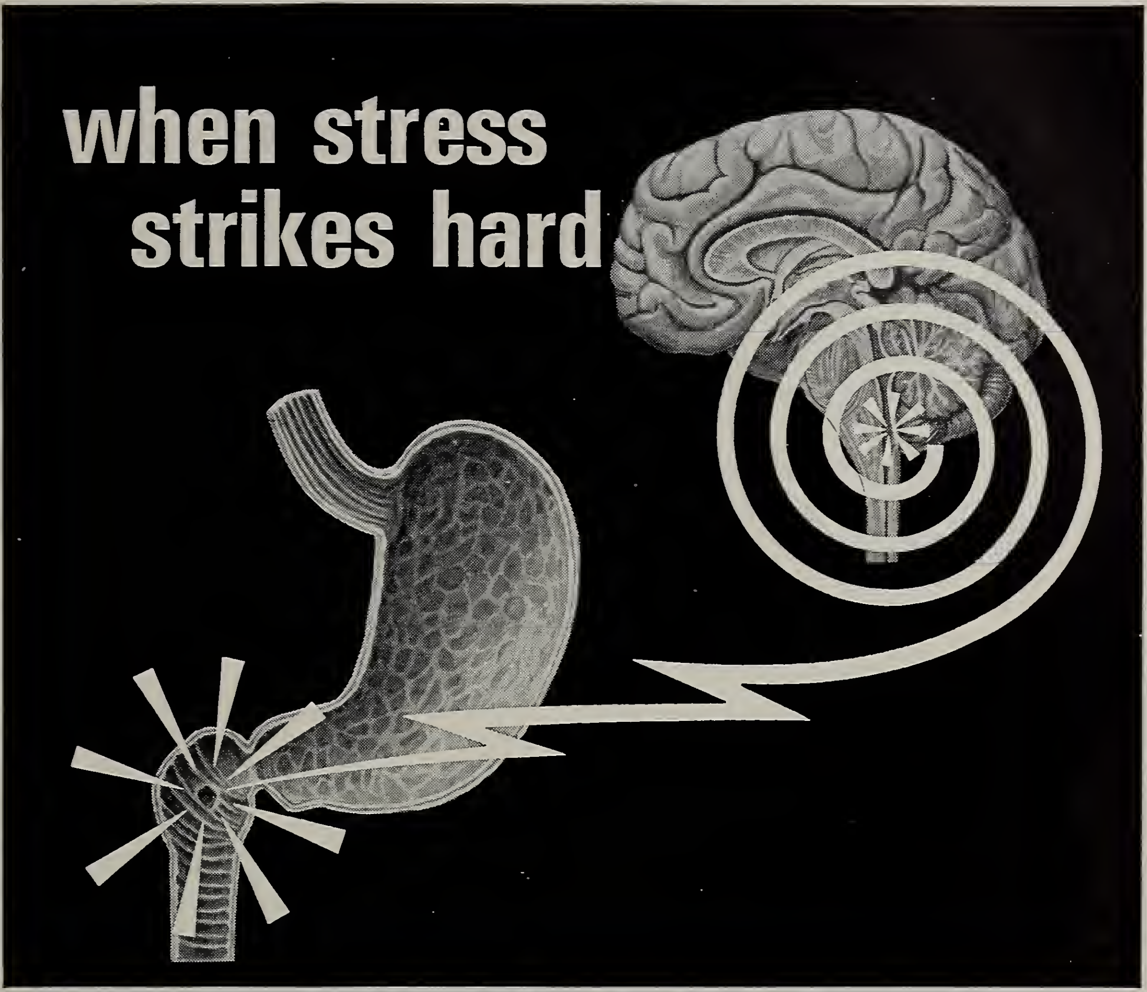
This book, specializing in brevity, portrays the dimensions and the fundamental concepts of the broad specialty of orthopedic surgery. It must be emphasized that this book has been written to introduce the reader to the various facets of the specialty, and it must not be anticipated that it will give details of treatment or other information that would be needed by the physician undertaking the treatment of a major musculo-skeletal entity. The book will prove useful to the medical students, general physicians and those in para-medical disciplines who desire to know more of the scope and diagnostic and therapeutic methods employed by orthopedists.

While there is little on the subject of skeletal system trauma, there is broader coverage of subjects such as low back pain, the arthritides and foot problems. Several entities are presented in a correlative manner, correlating the pathologic anatomy, roentgenographic features and clinical findings. In the second half of the book, the material presented relates to anatomical regions: the upper and lower extremities, and the various segments of the spine. A final chapter, termed "Orthopaedic Horizons," outlines some of the unsolved problems in orthopedics, particularly in the realms of surgery, diagnosis, and etiology. A glossary at the end of the book further indicates that this is an introductory treatise.

Physical features of the book are excellent, and the author's 158 illustrations have been exceedingly well reproduced.

This book is worthy of a place in the library of those great physicians, para-medical workers and medical students who desire to learn more about the fundamentals of orthopedics.

J. Vernon Luck, M.D.



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New Technique to Aid Infant Breathing

Mechanically assisting the breathing of a newborn infant has long presented difficulties.

Many babies die who might have survived if a way could have been found to keep them breathing in the first days after birth. Others survived, but suffered brain damage.

Five physicians report a technique in the July 19 *Journal of the American Medical Association* which in early trials has shown a high percentage of success in aiding infants with breathing difficulties.

The idea is simple: a soft plastic tube attached to a mechanical respirator is inserted through the baby's nose and into his trachea. It is kept there for several hours or days until the baby's body can fight off infection or drug imbalance and take over its own breathing.

Oxygen-enriched air with high humidity and at relatively high pressure is administered. The respirator's speed is increased for an infant's rapid breathing.

The difficult part of the procedure is the close attention which must be given the infant and the respirator throughout the long period of breathing assistance. The attention is equal to that given a surgical patient under anesthesia, the authors report.

This method of respiration has "important advantages" over inserting a breathing tube through a trachea incision, the report said.

"First, respirator treatment can be started simply and speedily. Second, it can easily be discontinued if the infant seems to improve."

Earlier attempts at assisting infant breathing were hampered by several factors. Most respirators designed for adults were not sensitive enough to respond to the faint breaths of such small patients.

To prevent the infant breathing out of phase with the respirator, it had been considered necessary to produce complete paralysis with the drug, curare. The authors eliminated the curare, and found that infants allowed their breathing to be adjusted by the respirator when the new technique was used.

Finally, the insertion of the tube through the nose, plus development of more sensitive infant respirators, eliminated need for trachea incisions.

The authors point out that they use more conservative treatment in many cases of respiratory distress syndrome (hyaline-membrane disease), including control of body temperature, provision of high-humidity, oxygen-enriched atmosphere, and administration of intravenous glucose and sodium bicarbonate.

"Many infants respond to these measures, but some do not; they become cyanotic, lethargic, and die. It is for these babies, we believe . . . that in-

(Continued on Page 40)

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New Technique to Aid Infant Breathing

(Continued from Page 38)

termittent positive pressure respiration has much to offer."

Newborn deaths due to simple drug depression should now be entirely preventable, the authors said. The infant can be given respiratory support until his body restores more normal chemical balance. Treatment in less common causes of severe respiratory trouble also should be effective, they said.

In the past three years, the five physicians report treating 26 infants. Eighteen survived, including one who weighed only 2.2 pounds at birth. Only one of the infants was reported to have suffered brain damage.

The authors of the report are D. Vernon Thomas, M.D., Grant Fletcher, M.D., Philip Sunshine, M.D., Irwin A. Schafer, M.D., and Marshall H. Klaus, M.D., all of the Stanford University Medical Center, Palo Alto, Calif.

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Medical Ethics to Be Discussed

Former Congressman Walter H. Judd, M.D., will be a luncheon speaker at the first National Congress on Medical Ethics and Professionalism, sponsored by the American Medical Association Saturday and Sunday, October 2 and 3, at the Drake Hotel in Chicago.

Dr. Judd's topic, *"Can the Best be Better?"* will outline accomplishments and deficiencies in the medical profession's standards for ethical deportment.

The opening session of the National Congress will feature James Z. Appel, M.D., president of the AMA, who will speak on *"Medicine—A Profession or a Business?";* Everett Hughes, Ph.D., sociologist, formerly of the University of Chicago who studied professionalism as it related to medicine during a period spent at the University of Kansas Medical Center; Russel B. Roth, M.D., of the AMA's Council on Medical Service, who will discuss *"The Transmutation of Economics to Medical Ethics,"* and James H. Berge, M.D., chairman of the AMA Judicial Council, who will outline the scope of the conference and the AMA's expanded program on medical ethics.

Also speaking on the October 2 program will be three physicians who serve as the investigating committee for the Judicial Council in "original jurisdiction" cases coming before the AMA. They are Drs. Arnold O. Swenson, Duluth, Minn.; Robert Mayo Tennery, Waxahachie, Texas, and William Y. Rial, Swarthmore, Pa.

Saturday afternoon will be devoted to workshop sessions. Handling of patient grievances and medical disciplinary procedures will be discussed.

On the Sunday program, speakers will include Wendell C. Stover, M.D., Boonville, Ind., chairman of the AMA Commission to Coordinate the Relationships of Medicine with Allied Health Professions and Services; Samuel P. Neuman, M.D., Denver, Colo., chairman of the AMA Committee on Osteopathy and Medicine; Attorney Edward L. Wright, who is chairman of the American Bar Association's committee preparing a revision of the legal profession's canon of ethics, and William H. Gordon, M.D., Lubbock, Texas, whose topic is *"Be a Physician First."*

Physicians wanting to attend the National Congress on Medical Ethics and Professionalism should write to Dr. James H. Berge, Chairman, Judicial Council, AMA, 535 N. Dearborn Street, Chicago, Illinois 60610. Early reservations are advised.

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C.A.G.P. Annual Scientific Assembly to Meet October 24-27 in Los Angeles

The California Academy of General Practice will hold its 1965 Scientific Assembly at the Statler-Hilton in Los Angeles on October 24-27. Emphasizing practical, everyday problems of medical practice, that meeting will bring together twenty outstanding speakers.

Doctors attending the meeting will have an opportunity to hear Hans Selye, director of Institute of Experimental Medicine and Surgery, University of Montreal; Surgeon Manuel E. Lichtenstein, Chicago; cardiologist Irvine H. Page, director of research, Cleveland Clinic Foundation; psychiatrist Bernice C. Sachs, Seattle; pediatrician Patrick Ongley, Mayo's; gynecologist Howard C. Stearns, Portland, Oregon.

On the program from Northern California are Eugene Farber, Mark Gorney, Don King, Felix O. Kolb, Earle M. Marsh, Sidney J. Sussman, and Donald Traeger. Southern California speakers are Harry F. Dietrich, E. Grey Dimond, Richard S. Farr, George C. Griffith, James McClure, Telfer B. Reynolds, and Paul A. Shea.

Horace F. Sharrocks, Sebastopol, current president of the Academy, will open the meeting. J. Blair Pace, San Diego, will take over as president at the final session. Robert L. Hippen, San Diego, is program chairman for the event.

Anyone wishing a complete program or hotel reservation information should write California Academy of General Practice, 9 First Street, San Francisco 5. All members of the California Medical Association are invited to attend the meeting. There is a $10 registration fee for non-members of the Academy, payable at the time of registration.

Is the Autopsy Out of Date?

The autopsy, once a major part of medical teaching and investigation, has fallen on hard times. Thousands of autopsies are performed every year, but they no longer occupy the central place in medicine that they once did.

There are a number of reasons, including the development of laboratory methods for diagnosing disease, the shortage of pathologists' time, and a general shift in emphasis in medical teaching and research.

Few, if any, physicians would want to eliminate autopsies entirely, but many medical authorities are requesting the need for the number that are performed.

Is the postmortem examination thus an outworn relic from the past? No, indeed, say five pathologists and a clinician in the September 6 *Journal of the American Medical Association.* However, they offer several suggestions for improving the autopsy.

During life, the patient is studied with the latest,

(Continued on Page 21)

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Is the Autopsy Out of Date?

(Continued from Page 14)

most up-to-date medical procedures, points out Joseph F. A. McManus, M.D., of the Department of Pathology, Indiana University School of Medicine, Bloomington. If the patient dies, however, the autopsy is often a superficial procedure that has been unchanged for a half century or more.

Two changes could improve the autopsy, points out a *Journal* editorial. The first is to restore the careful, detailed investigation that helps make it a research procedure. This may mean reducing the number of autopsies.

The second needed change is to "restore the autopsy to its rightful place as a teaching instrument," the editorial said.

"Through autopsies the pathologist can answer various specific questions and provide simple 'factual' data important for the physician, the patient's family, and the statistician. For example, did the patient have peritonitis following an operation? Was a sudden death due to an embolism? Was a lung tumor primary or metastic? Answers to such questions do not constitute 'science,' they do not advance conceptual or general knowledge, but they help the overall care of patients."

The autopsy is uniquely suited to study an individual disease, said Milton G. Bohrod, M.D., of the Department of Pathology, Rochester, N.Y., General Hospital.

"Every death corresponds to a failure, either of the individual physician, or, more commonly, of medicine as a whole. Every necropsy (autopsy) represents a last attempt to solve the enigma of the individual illness," he said.

Autopsies on all deaths probably should be done in teaching and clinical research centers, said Sidney C. Madden, M.D., of the Department of Pathology, School of Medicine, University of California, Los Angeles. This ideal cannot be reached in non-teaching hospitals, he said. The goal then must be selection of cases which yield the most useful information.

"Finally, the question can be asked, who is going to do autopsies?" said Charles S. Davidson, M.D., of the Thorndike Memorial Laboratory, Boston City Hospital, Boston, Mass. "Many pathologists nowadays have really become molecular biologists and are no longer interested in the autopsy and in pathologic anatomy.

"In conclusion, I am sure that we cannot give up the autopsy," he said. "It is absolutely necessary, but it must seek its place among all the various methods of study of the patient, of groups of patients, in teaching, or in medical research."

Other symposium participants were J. Beach Howard, M.D., Department of Pathology, Cleveland Clinic, Cleveland, Ohio, and Alfred Angrist, M.D., Department of Pathology, Albert Einstein College of Medicine, New York City.

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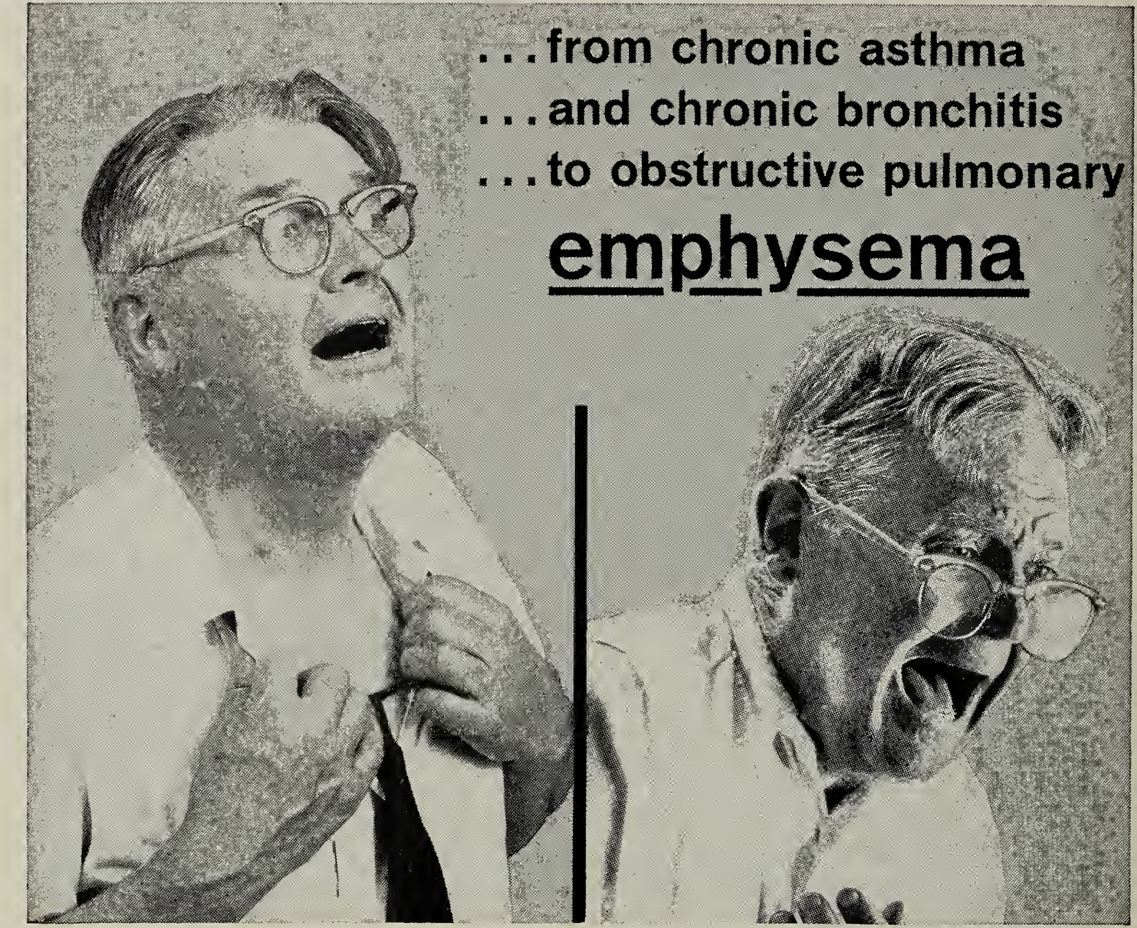

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1. Boren, H. G.: M. Clin. North America 43:48 (Jan.) 1959.
2. Jackson, R. H., et al.: Dis. Chest 45:75-85 (Jan.) 1964.

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Multiple Pregnancy Care Outlined

There are extra risks to both mother and infants in a multiple birth.

These hazards can be minimized, however, if a well-prepared medical team anticipates the problems of a multiple delivery, say three Chicago physicians. They outline their system of hospital care of the mother in the August 9 *Journal of the American Medical Association.* The authors are Emmanuel A. Friedman, M.D., M.Sc.D., William M. Alpern, M.D., and Allan G. Charles, M.D., of Michael Reese Hospital and Medical Center, and the Chicago Medical School, Chicago.

To allow the mother as much rest as possible, she is admitted to the hospital well before labor is expected. She is put to bed, and her diet is supplemented, if necessary.

Meanwhile, the hospital's largest available delivery area is prepared. An adequate stock of cross-matched whole blood is assembled. A catheter is inserted into a vein of the mother—just in case blood, anesthetics, etc., are needed.

"It can be a rather difficult procedure, consuming valuable time, to do a simple venipuncture on a collapsed vein when the patient is in shock," the authors point out.

The mother is given oxygen, but pain-killing analgesics are kept to a minimum because of their possible effect on the infants. More than half the babies born in multiple pregnancies are premature by weight. The choice of anesthesia is made carefully, for the small baby does poorly when the mother is given excessive inhalation agents.

One of the hazards of a multiple pregnancy is that the second baby may be in a position which complicates delivery.

"As a general rule, it is probably wisest to allow the first infant to be delivered spontaneously . . . with the mother under local, regional block, or light inhalation anesthesia," the report said.

The second baby's position is determined quickly after the first birth, and its delivery is managed according to the circumstances, Great care is important, for statistics show that second twins have a lower survival rate at birth then the firstborn.

After the delivery, doctors watch for possible damage to the mother's internal organs, and guard against shock. A series of tests are made later on the mother and the infants.

"Ideally, closely supervised aftercare (of the mother) in a well-staffed recovery area will provide the kind of observation that will detect the first clinical signs of deterioration. There can be no substitue for vigilance," the report said.

The result of such a carefully pre-planned program is that risks can be greatly reduced for the mother and her babies, the report concluded.

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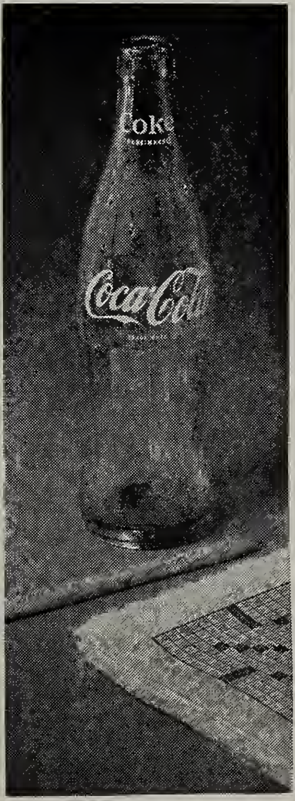
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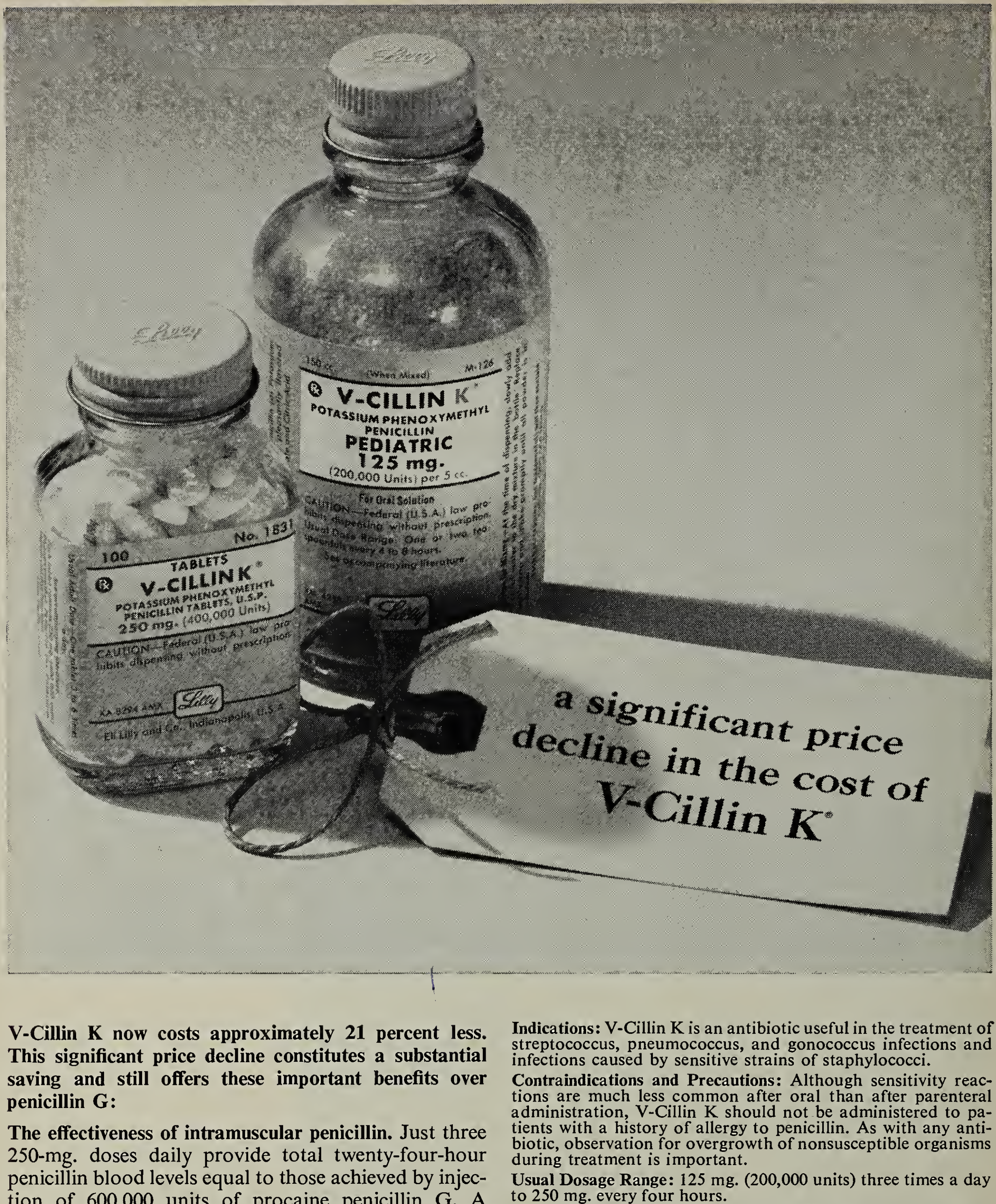

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The Further Education of the Graduate Physician

IGNACIO CHÁVEZ, M.D., *Mexico City*

WHAT DOES IT MEAN to teach medicine today? To squeeze the whole world of knowledge we possess; to extract what is fundamental, what is basic, limiting ourselves to the indispensable; to train a student in the complicated techniques of modern methods of study, educate his spirit to make a man of science out of him, wise in observation, aware in research, accurate in his reasoning—and all this without depriving him, as a clinician, of the ability to apply his knowledge. To achieve all this over a period of a few years, while the youth becomes a man, and then send him out into the world with an education and a mentality in harmony with our times—let us agree that this is a grand educational task, a fine challenge to the most optimistic teacher.

The difficulty of teaching medicine began to be faintly apparent in the Sixteenth Century, when the spirit of the Renaissance broke the bonds of dogma and scholastic prejudice and opened the path of science, of seeing, of observing in order to understand, of questioning nature directly, rather than seeking for the answer in an old book of Galen. Leonardo and Vesalius were the first to open the breach. Through this breach there passed after them the great renovators, from Harvey to Morgagni.

Thus the difficulty of teaching medicine grew slowly greater as the Nineteenth Century drew nearer, the century when scientific medicine as we understand it made its appearance, and had us, with Laennec, practice the physical exploration of the sick; register, with Ludwig and with Bernard, their organic functions; taught us, with Pasteur and with Koch, to observe the intimacy of their immunological reactions, and to predetermine, with Virchow, the magnitude of those organic lesions caused by disease.

This whole enormous common reserve of knowledge required, in order to be taught, lengthened studies and more complicated explorations, the provision of laboratories and the management of equipment. Upon the subsequent appearance, at the beginning of the Twentieth Century, of radiology, electrocardiography, a new aseptic surgery and biochemical laboratories, there also appeared, it is true, new complications in the teaching of future physicians and surgeons, but the complications did not go beyond the insuperable. In fact one did not breathe the air of anguish in schools of medicine before the nineteen twenties.

However, from that time up until now, in the space of what is hardly two generations, the change is impressive. This is particularly true of the years between the end of the Second World War and today. The giddy career of the sciences and of different techniques, ever more precise, ever more complex and ever more indispensable, have made of medicine a world of knowledge, the domination of which is far beyond all human possibility. And day after day new material and new discoveries continue to accumulate in an inexhaustible flood upon this already gigantic mass.

It is impossible to teach all this. One can only select what is fundamental, what is demonstrably true or, at most, what is highly promising; that is,

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Presented at the University of Southern California before the members of Salerni Collegium, April 13, 1964.

Dr. Chávez is Rector of the University of Mexico, Mexico City, and the founder and an honorary director of the Instituto Nacional de Cardiologia.

one can only weld together a solid and coherent structure of basic knowledge; and that is all that a school of medicine can hope to achieve. Subsequently there will be specialization to ensure total ability in a chosen field, and then subspecialization to allow the fullest possible exploration of a limited theme; and finally there will be research, the requisite for advance and for the addition of new material to our world of knowledge.

Thus medicine progresses, at a rate that can only be considered fantastic. Teaching, however, is not keeping pace with progress. It cannot do so. The anguished atmosphere we breathe derives from the very awareness of the distance, a distance that grows greater every day, between what is known and what is taught. And together with this, there is also the awareness of the difficulty, the immense difficulty, of halting this tendency. How can this distance be shortened? Here we have the problem.

There are countries, such as Mexico, where to the problem of the growth in medical knowledge we must add the problem of the impressive increase in the number of students desirous of studying the subject. Thus the difficulties of teaching grow in a geometric progression.

In one way or another, in different degrees of acuteness, the problem exists throughout the world. It is a universal phenomenon, the fruit of our times. But there is yet still more, something further to complicate the lives of our schools of medicine, something which although it did indeed exist in the past, but only today, only in our times, has come to the surface and become one of our primary preoccupations.

While medicine progressed but slowly, employing relatively simple techniques, the physician or surgeon could complete or renew his studies throughout the course of his professional life. This he did alone, depending upon his reading and the accumulation of experience.

Keeping Up-to-Date

Today such efforts must be considered rudimentary. And thus we face the problem: How may we ensure that the medical school graduate who goes out into the world with a modern equipment of knowledge shall not allow it to become rusty and out-of-date? How may we ensure that he does not become old-fashioned, becoming a public danger? What can we do to keep him up-to-date and ensure his continued education?

Such is the challenge of our times. It is a challenge that concerns those young men now leaving our hands, as well as the older physicians who have spent many long years in the profession. And we might enquire what would be the result if this latter group should be examined.

One day a French clinician asked a curious question: If a doctor, in the style of a fairy tale, had fallen asleep in 1934 and awakened today, how would he regard the panorama of modern medicine? Would he even begin to understand it?

We are all capable of elaborating upon the answer. His surprise, of course, would approach astonishment. Theories and methods of exploration, diagnoses and treatments that he had neither known nor imagined in his day, are, he would find, all taken quite as a matter of course today. He would learn of catheterization of the heart, endoscopic examination of a wide variety of organs, selective angiocardiography, biopsy of all the viscera including the heart, tests employing radioactive isotopes and the determination of enzymes and hormones of which he had known nothing; he would hear of surgical repair of the heart, using plastic materials and artificial valves, the grafting of large vessels, the use of mechanical pumps in substitution for the heart and lungs, and of filters employed as artificial kidneys, of the substitution of live organs, overcoming the problem of foreign body intolerance—he would learn of all this that in "his time" appeared to be impossible and is today put into practice daily.

He would also be confronted by the miracle of antibiotics and by the cure of both meningitis and endocarditis, previously called incurable; he would note the beginning of control of tuberculosis and leprosy, and the almost complete disappearance of certain medical specialties, now unnecessary. He would observe large populations protected against poliomyelitis, and he would see social scourges such as rheumatic fever and salmonellosis, amebiasis and *mal de pinto* greatly diminished if not completely dominated. He would observe diabetes controlled and arterial hypertension overcome. He would see infant mortality reduced to a minimum and the expectancy of life increased to a maximum, to some 72 years. And, as a kind of irony, he would discover that man is now concerned about space medicine, in expectation of the need for interplanetary travel!

Taken together, all of this constitutes a proper motive for pride for contemporary medicine, but it also establishes the degree of danger. What would occur if this physician, after being asleep for some 30 years, wished to practice again? Consider the danger attendant upon his treating patients according to the knowledge and procedures of the past.

This then, although less spectacular, is the drama of many members of the medical profession who, over long years of practice, have never renewed their scientific equipment, and who live and think and work as they were accustomed to in "the old days." It is true that even without studying they become fragmentarily aware of certain advances. The press, the radio, the pharmaceutical salesmen who bring technical advertisements of the new drugs to their consulting rooms, the commercial house magazines that are freely offered, the whole apparatus of modern publicity oblige them to come into contact with certain novelties. But we shall agree that this flood of information comes to them along an empirical road and is received uncritically and in a disordered fashion. Without ever realizing it, what they practice is no longer scientific medicine; it is hardly even a trade.

Personal Drama and a Social Problem

It is true enough that this is a personal drama, but it is also a social problem. It concerns us all in a moment when it is a danger for many. The case I mention of the older physician who no longer studies is much more common than might appear. Ten years of neglect are enough, in the medical profession, to become out-of-date. And within these limits there are a great many who fall.

The medical profession as a whole has understood the problem in these terms, particularly since the end of the war, and has multiplied the opportunities for practicing physicians to study. Many methods have been employed—lectures, monographic courses, symposia, periodic meetings of scientific societies. There are congresses of all kinds, bulletins and reviews, special television and radio programs; all the various media of communication have been tried. Year after year, more and greater efforts are made; and to achieve success, medical schools, hospitals, scientific societies and research institutes all collaborate. In the present year alone, in these United States, some one thousand, two hundred and sixty-four courses of further education have been offered by some two hundred and sixty-seven institutions.

However, despite the enormous effort, the problem grows at the same rate as medical science advances, and there are many, very many, physicians who have not responded to the call, and who have cut themselves off from the whole scientific world.

The obstacles vary greatly according to the distinct conditions. When the physician lives in a city where there is a medical school or an important hospital, all is easy for him. But when he lives in a small town or is settled in some isolated spot; when his economic situation is such that he cannot travel in search of instruction; when he is old, or tired; above all when he no longer feels either hunger or thirst for renewal, it is then that there seems to be no simple, efficient way to undertake his further education. One such physician once said to me dispiritedly, "The train has left me behind."

If this only occurred with age, there would be at least, an excuse in the biological fact. But the gravity of the problem resides in the fact that this is not an ill peculiar to men advanced in years. For this reason it is necessary to try to apply the remedy from the beginning, before any signs of spiritual devastation are to be seen. The remedy must be applied during youth, when the mind is undergoing its intellectual formation. It is then that we must teach the young how to study, must help them develop a taste for learning. Rather than teach a certain quantity of science, we must teach them to love it. When one has this love, the rest shall be given, as the Bible has it.

The Seed of Continuing Education

Here, then, is the key to further education. It lies in preparing for it from student days onward. The student who does not content himself with the word of the teacher when learning, but who seeks out the sources for himself; the student who learns to use books and to make notes of his reading; he who becomes accustomed to summarizing them, ordering them and evaluating them whether according to his own critical judgment or according to a scheme that clarifies or unites them; the student who is not content just to know, but who learns how to increase or modify his knowledge—such a student is protected against changes in ideas and fitted to understand the advances of the morrow. Such a student runs no risk of seeing the knowledge that he was given in his medical school grow out-of-date or simply rot.

In the National Institute of Cardiology in Mexico, where we accept young physicians from all over the world to provide them with a thorough grounding in the specialty, we see eloquent examples. Once the habit of study is created, once the habit of forming a personal judgment and of submitting it to the criticism of fellow workers is achieved, we see these young men, their stay with us completed, off to establish themselves in the provinces or abroad, frequently return to refresh their knowledge. There are some who make a short trip every Thursday to attend the general anatomo-clinical sessions; there are others who come from a distance, or from other countries, every year to repeat monographic courses. Their love for science, like the Muslem's love for his religion, causes them to turn their faces periodically towards their Mecca.

Thus this has become one of the fundamental obligations of every medical school. Previously it was enough to turn out a good physician; today, confronted by the perspective of rapid change and the threat of professional deterioration, medical schools must prepare their students for the future, teaching them to renovate their knowledge.

In this way the further education of the practitioner will be greatly facilitated. There will be no reason for it to be limited to the annual addition of a few novelties. Indeed, it is not a process of accumulation but of change, of the renovation of doctrines. When something new is added, it is almost invariably necessary to get rid of something else. And this, in the field of ideas, is not easy. It requires an enormous effort to abandon those ideas which have accompanied us throughout our lives. It might even seem that some of them crystallize, become petrified, reach the point where they become an integral part of our beings. If it is difficult to learn after a certain age, to "unlearn" is even more difficult.

Wide Range of Possibilities

I shall not go into all the details of what can be done in the field of further education. The Dryer Report is a magnificent study of what can be and what must be done. In it we find laid out the whole range of possibilities, from the Socratic dialogue and the teaching lecture to closed-circuit television and the help to be given by electronic computers.

It is not given to all of us to do the same, whether for reasons that lie in the field of ideas or because of the difference of material facilities. Each country has its own philosophy of education, and we must not fall into the error of believing that tradition is invariably an empty formula or necessarily a brake upon progress. We in Mexico are attracted rather more by simpler formulae, without any great technical complications, formulae in which the idea of personal contact is dominant. Education at a distance may be good, but only when the other solution, that of teacher-student contact, is out of the question. So long as physicians can be drawn to medical schools and to hospitals, so long as instead of offering them lessons over the radio one can take them to the bedside of a patient or to a laboratory bench, so long as teaching can be enlivened by the presence and personality of the teacher—so long as these things can be done, we shall always be inclined towards this kind of education. The other solution we shall reserve for the situation of Mahomet when he could not go to the mountain.

The Medical School of the National University of Mexico has only recently completed the reorganization of the structure of further education, an establishment on four levels. Beginning at the bottom level, it is concerned to help very large numbers toward a periodic renovation of knowledge, and it goes up to cover the training of specialists in limited numbers and of academic standing, and, at the highest levels, includes the degree of master and of doctor in order to satisfy the needs of teaching and research.

At each level, insofar as they deal with medical rather than purely scientific subjects, the major preoccupation of the school is to ensure the conservation of the Hippocratic spirit in our teaching; to ensure that the scientific medicine that we teach does not suffocate clinical medicine; that the spirit of research shall not supplant the spirit of observation, but rather complement it; that interest in medicine as such shall not override interest in the patient; that the wise physician shall never impede the formation of the cultivated physician. If it is the former, with his science, who ensures the efficacy of medicine, it is the latter, with his fine spirit, who ennobles and sometimes sanctifies the profession.

It is a task such as this, gentlemen members of Salerni Collegium, noble, important, and generous, that you are undertaking in benefit of the University of Southern California. I am confident that the fruits that will be gathered, in the form of yet more scientifically trained doctors, and of better health, improved welfare and greater happiness for your fellow citizens, will be in accord with the generosity of your efforts.

University of Mexico, Mexico City, D. F.

Family Homeostasis and the Physician

DON D. JACKSON, M.D., *Palo Alto*

■ *Physical illness, including psychosomatic disorders, often play an unexpected role in maintaining emotional balances within the family. The outbreak of such disorders, conversely, can be utilized by the physician as a barometer of family emotional difficulties.*

RECENTLY, an English general practitioner published a modest little book[4] in which he noted (and presented in graphic form) that the families he was treating in a small English industrial town tended to have illnesses in clusters. He had devised a system whereby he kept records of each family on a single card, with the individual family members listed vertically and the time, in months, marked off horizontally, so that he could note by glancing at the card not only the usual data of who had what illness when, but that a family tended to have an agglomeration of illnesses in one time period. In general, the illnesses that clustered did not include such complaints as broken legs but were either "psychosomatic," that is, headaches, stomach upsets and the like, or were infectious diseases, some of which he felt were not necessarily highly contagious. He documented that in some of his families an individual could have a cold without the other members catching it. In some of his families, when one person got a cold, some other family members were apt to join him.

This observation of the supra-individual effect of the family on its members goes along with what has been one of my primary interests for many years, the question of family homeostasis. In 1954, I wrote a paper[2] which was based on my first two and a half years in the private practice of psychiatry in Palo Alto. I had come here from a training center where very sick psychiatric patients were treated largely by intensive individual psychotherapy. With an ambulatory practice in a relatively small town, I discovered that treating an individual patient meant having contact with his family (which I was not used to), and one of my early cases turned out badly:

> I was seeing a young housewife for a fairly acute depression, and she seemed to be responding rather well. I had met her husband briefly when I had first seen her in the hospital and had spoken with him a few times over the phone. Unfortunately, it did not dawn on me to invite him in, nor especially did it occur to me to see this couple together. Just when I thought the patient was getting out of the woods, I

The author is director of the Mental Research Institute, Palo Alto, and clinical associate professor of psychiatry, Stanford University School of Medicine, Palo Alto.

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began getting phone calls from the husband, usually in the evening, asking about his wife's treatment and expressing concern that she was getting worse. His concern caused me concern, because I thought I must be missing the boat; but it did not occur to me for several weeks that the boat I was missing was his and not hers. The wife was indeed improving, but her husband was beginning to have trouble. One morning, the wife informed me that her husband had lost his job and that she was quite surprised at this since he had the reputation of being a successful, bright young man. I called him and asked him to come in and see me, but he refused, stating that he was too busy looking for work and that his wife was the real problem. It was clear from his tone that he was not feeling very cordial toward me. The following evening, I read of his suicide in the paper. His wife was spending a few days with relatives out of town, and, unwittingly, we all had deserted him.

Since this initial experience, I have had literally hundreds of clear-cut situations involving an upset in one family member caused by a change in the emotional status of another member. Some of these cases I have dealt with personally, some have been discussed with colleagues and others have occurred during the course of supervision of psychiatric residents. However, my observations have not been limited to typical "psychiatric problems." As a member of the Palo Alto Medical Clinic, I had access to medical, and occasionally surgical, cases that the ordinary psychiatrist might not encounter. It became apparent to me that homeostatic imbalance can involve physical illness as well as emotional ones.

The concept of homeostasis stems from Cannon's epoch-making physiological studies, and from the earlier efforts of Claude Bernard with his concepts of *"le milieux interieur."* Homeostasis is not synonymous with static balance. It implies, instead, that a system is in operation and that processes are going on which keep the system relatively stable. Too often the concept of homeostasis is confused with a static notion like balance, but simple balance and imbalance do not convey the subtlety of interdependent, active processes intended by the term homeostasis.

We can make our notion of family homeostasis specific by describing the family as an "error-activated system" which seems to react to inputs that are not in accordance with its baseline or rules. A simple furnace thermostat is a good analogy: Essential to the concept of corrective feedback is the distinction between deviation-counteraction and deviation-amplification (negative and positive feedback, respectively). The usual household thermostat responds to increased heat by shutting off the furnace when the temperature reaches, say, 68 degrees. This is a deviation-counteracting system. However, if increased heat instead *activated* the furnace to produce even more heat, this would be an example of positive feedback and the result would be a deviation-amplifying system which would produce too much heat, large fuel bills, and soon a ruined furnace.

We know there are small (for example, family) and large (for example, nation) human systems that react in deviation-amplifying ways. For example, nation *A* and nation *B* have a naval treaty limiting both to certain numbers of capital ships. Nation *A* gets worried about *B,* so it builds an extra destroyer to patrol *B's* coast. Alarmed and outraged, *B* builds a cruiser to guard against *A's* destroyer. Whereupon *A* retaliates with the launching of a battleship, and on they go to war.

So too there are family wars. If the husband and wife have what we call a symmetrical relationship (that is, one based on the need to prove equality), then each will feel that he has the right to determine the nature of their relationship: If the wife buys a five-dollar pair of hose, the husband will have to get a necktie; if the husband lets the kids stay up late for a television program, the wife will let them stay up to watch the one after that. Obviously in such a relationship situation, ordinary "family work," let alone pleasant interaction, cannot occur; and, as the situation worsens, just as with nations *A* and *B,* the spouses will blame each other until divorce, desertion or disaster is the inevitable outcome.

From this example we can see that if the family is to remain a family unit, negative feedback, or deviation-counteracting mechanisms, must play a large part. The average family absorbs "inputs" from its social, economic, and community environment, as well as from the behavior of individual members and the inevitable changes brought by time; still the family that endures counteracts these deviations and maintains its organization with a facility which makes the household thermostat appear as child's play.

The problem is that this baseline may involve psychiatric symptom manifestation on the part of one family member; and an "error" or deviation" in the form of the patient's improvement may, as I have shown in my first example, lead to strong counteraction from other family members. Thus, the rest of the family may insist that the identified patient is still "really" sick, even going to great lengths to prove this or make it possible. My experience has convinced me that one does not assume that the identified patient lives in a vacuum; to the contrary, his improvement may result in family resistance, physical or emotional symptoms in other family members, or even the dissolution of the family. While one should not seek to preserve such a homeostatic balance, neither can one ignore its obvious practical implications. For example:

(a) A husband urged his wife into psychotherapy because of her frigidity. After several months of therapy she felt less sexually inhibited, whereupon the husband became impotent.

(b) A young woman with *anorexia nervosa* was persuaded to enter psychotherapy by her husband. Following a period of intense, rather dangerous, acting out, she began to relate more intimately to her husband. The husband's initial pleasure at her response was marred by his developing a duodenal ulcer.[2]

(c) During a family interview the patient's brother, encouraged by his relationship to the therapist, tentatively ventured that his mother might be a little hypocritical in her dealings with the patient. The father, with a liberal sprinkling of alibis for her, agreed with the son and his wife quietly accepted the verdict but with an air of "that's what I get for trying my best." Unfortunately, the therapist had the impression that the mother was accepting the comment and since it was near the end of the session nothing further was done with it.

Early the following morning the mother was taken to the hospital for an emergency cholecystectomy although she had had no previous history of gall bladder distress or of stones. Upon her return home the father was put in hospital for a coronary attack and in the midst of this psychosomatic melee the brother, who had initially introduced the damaging remark, had three automobile accidents, all of a similar nature: He simply crashed into the rear of the car ahead. At this point the family decided that they could no longer afford our expert help and placed the patient in a state hospital.

(d) A young man was sent to the psychiatrist by his wife because of three recent episodes of infidelity. It became apparent during the interview that (1) he had become successful recently after some years of working toward it in dubious battle; (2) his wife had recently had their third child, a boy, and the patient was the third child in his family. The wife had a younger brother who was the favorite in her family and who was referred to as a "juvenile delinquent"; (3) the wife was unbelievably naive or else she was pushing the patient toward his extracurricular activity; (4) the patient did all that one can do and still manage to remain unaware of it, in order to signal to his wife that he was being unfaithful.

The patient was asked to bring his wife to the next visit since his cure lay largely in her hands. This request was made since it was obvious that she felt unimportant and also, in the typical manner of the injured party, felt uninvolved in his sins. Although she came initially with the attitude of "anything to help George get over this nasty business," by the end of the second session she was able to accept the comment that her finger was also in this particular pie. They were seen altogether for only nine sessions with two follow-up visits and made remarkable progress. The brevity of the therapy was partly pecuniary and partly because of the amount of work they did together between sessions.[4]

If the family operates as an error-activated system, then this fact should be observable and testable. During the many years of concentration on the individual, psychiatrists, and psychologists were neither concerned with nor aware of the tremendous impact of family forces. Indeed, until the publication of Richardson's remarkable book, *Patients have Families,*[5] one could learn more about the family from fiction than from a psychiatric textbook. The study of the family has burgeoned since World War II, and this seems to have been stimulated both by the general scientific emphasis on systems (cybernetics, for instance), and by the specific experiences that therapists were having with schizophrenic patients. As long as schizophrenia was considered an organic disorder and a rather hopeless one, the therapist did little in the way of treating schizophrenic patients other than isolate them in large steel and concrete mausoleums euphemistically called hospitals. The experience of psychiatrists during World War II was often that acutely psychotic patients showed remarkable ability to recover quickly, a phenomenon that caused many therapists, on returning to civilian practice, to continue an interest in treating patients with schizophrenia. They quickly realized that there was something unusual about the patient's family, and the early family theories of Lidz, Bowen, Batson, Jackson and others were all based on the study of families of schizophrenic patients. Now there are a number of centers in the United States, including the Mental Research Institute in Palo Alto, where the primary focus of research is on the family.

Evidence that the family is an error-activated system, and that it has specific homeostatic mechanisms, is not limited to the clinical experience of seeing a patient's improvement lead to an upset in another family member; it also is beginning to come from experimental work. For example, Haley[1] has shown with the aid of a computer that the simple measurement of who talks after whom in a family reveals distinct patterns for each family, and these patterns are not only extraordinarily consistent, but are different in "normal" and "abnormal" families. In a sample of a hundred families (50 normal and 50 abnormal), the abnormal families used far fewer patterns of "who talks after whom," and the difference between the two groups was significant at $p=.00003$. On retests as long as six months to a year later, abnormal families maintained to within a few percentage points exactly the sequences they had established previously, whereas normals varied.

This confirms two clinical hypotheses: (1) that families in general establish a baseline, a set of rules, or something analogous to the setting of the furnace thermostat at a certain desired temperature, and that they maintain this consistency over time regardless of the innumerable assaults which must be made on it both by the environment and the individual members; (2) that families which contain a deviant member (this sample includes families of psychiatric patients, of patients with ulcerative colitis, of underachieving sons, and a wide variety of other symptom bearers) are extremely fixed in their homeostatic patterns and do not "permit" deviation from such patterns.

Thus, the hunches of clinicians have once again turned out to be correct. However, none of us suspected that the family was quite as rigid a system as it appears to be—although most of us who live in a family realize that we can be quite different outside the family than we might be at home. Any of you who have attended a convention may have had cause to marvel at your own and others' behavior away from the supports and constraints of usual surroundings.

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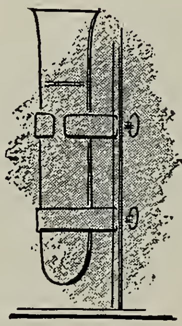

Operations on the Colon

The Role of Antibiotics in Preoperative Preparation

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■ *A study was carried out on 183 patients in an attempt to evaluate the role of antibiotics in the preoperative preparation of the colon.*

Kanamycin, neomycin and a placebo were administered in a double-blind fashion during a 72-hour period preceding operation. In addition, mechanical cleansing of the bowel was done in all cases.

Considering only the criteria of mortality and the incidence of postoperative wound and peritoneal infections in this preliminary report there was no apparent significant difference between patients receiving antibiotics and those receiving a placebo.

INTESTINAL "sterilization" has been common practice for more than two decades, but there are still many unresolved questions about preoperative preparation of the colon. The purpose of using chemotherapeutic agents and antibiotics before operations on the rectum and colon is to reduce the risk of postoperative infection. Many investigators attribute the improved morbidity and mortality rates in recent years largely to this practice, although not overlooking the contribution of improved anesthesia and other refinements in preoperative and postoperative management.

In some animal studies, antimicrobial drugs have also been shown to favor the healing at the site of intestinal anastomosis and to increase survival when segments of bowel are devascularized.[3,8] It is extremely difficult, however, to evaluate these potential advantages in clinical situations.

On the other hand the potential disadvantages or risks of antimicrobial therapy have recently received increased attention.[9,11] Foremost is the possibility of developing drug-resistant strains of bacteria and superinfections. This risk may vary, depending upon the predominant strains in the environment. Staphylococcal enterocolitis is a serious complication related to the suppression of the normal bacterial flora in the intestinal tract. Although commonly associated with such broad spectrum antibiotics as the tetracyclines, this complication may also occur following the use of oral neomycin and kanamycin, two of the agents commonly used in preoperative preparation today.[4]

Recently it was suggested that the "sterilized" bowel may be more vulnerable to the growth of recurrent tumor at the suture line. Vink[10] and Cohn[2] in studies of Brown-Pearce tumors in rabbits, showed that use of intestinal antibiotics was associated with an increase in the rate of metastasis as well as the incidence of recurrence at the site of anastomosis in the colon. However, there is as yet no indication of similar effect in humans.

In an attempt to clarify some of these problems a study was carried out to evaluate the preoperative use of antibiotics as compared with only mechanical cleansing of the colon.

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Method

The study was in two phases. In Phase I, five groups of 20 patients each were given two different dosage regimens of kanamycin and of neomycin and a placebo. Capsules identical in appearance were prepared, containing variously 350 mg of neomycin base, 500 mg of neomycin base, 350 mg of kanamycin base, 500 mg of kanamycin base, or a placebo.* (The base equivalent of 500 mg of the sulfate of either drug is 350 mg base.) Drugs were dispensed to each patient in a double-blind fashion. An envelope system set up from a random numbers table was used to insure random administration.

The antibiotic or placebo was started 72 hours before operation on the following schedule: two capsules every hour for four hours, followed by two capsules every six hours until midnight of the day before operation.

The code for these five groups was not broken until the clinical and bacteriological evaluations had been completed on all patients.

In Phase II, four groups of 25 patients were given drugs which were coded as A, B, C or D. Two of the drug groups consisted of 500 mg of kanamycin sulfate and two groups consisted of placebo in identical capsules. To assure the capsules were given at random, the same code system used in Phase I was followed. Two capsules of each preparation were given every hour for four hours, starting 72 hours before operation. This was followed by three capsules every six hours until the midnight before operation. No other preoperative antibiotic therapy was given unless specifically indicated (for pulmonary or urinary tract infection or the like). Two patients in Group A, one in Group C, and one patient in Group D received other antibiotics during the week preceding operation. One additional patient in Group C received sulfasoxazole (Gantrisin®) during this period. During the postoperative period, antibiotics were administered only when specifically indicated by the occurrence of some infection. The cases were evenly distributed among the four groups in which a possibility existed that preoperative or postoperative antibiotics might have predisposed to the occurrence of wound or peritoneal infection.

In addition to the coded drugs, all patients in Phase I and Phase II received the following regimen for mechanical cleansing of the bowel:

- A low residue diet was started three days before operation.
- A liquid diet was given on the day before operation.
- 60 ml of castor oil was administered (except to patients with ulcerative colitis) with the first dose of the drug and repeated at noon on the day before operation.
- The majority of the patients (but not those with ulcerative colitis) received tap water enemas during the afternoon or evening of the day preceding operation.

In the Phase II study, five patients were excluded because, for one reason or another, the intended operation was not carried out. Four additional patients were excluded because clinical follow-up and bacteriological analysis were not completed. By coincidence, each of the four groups had one of these patients. Consequently, the code for this phase has not been broken to insure an unbiased analysis of the final results.

Patient Selection

Any patient with a known or suspected lesion of the colon or rectum was admitted to the study if the proposed operation could be delayed for the three days required for the preoperative regimen. Patients with any significant degree of intestinal obstruction were excluded. Also excluded were patients in whom colostomy was contemplated in advance, lest including them should introduce a large number of cases in which the colon was incised within the peritoneal cavity.

The age distribution of the four groups in Phase II is shown in Table 1. It was comparable with the age incidence in Phase I. Detailed clinical data on Phase I patients have been previously reported by Gaylor, Clarke, Kudinoff and Finegold.[5]

Among indications for operation, malignant disease was predominant. The kinds of cases were spread uniformly in all four groups except for a relatively high proportion of benign lesions in Group B.

The types of operative procedures performed also were fairly evenly distributed among the four groups. Most of the operations were performed by members of the senior resident staff. An "open technique" was used for colon resection and anastomosis. The total of 91 operations included only one colostomy, carried out in a Group D

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*Bristol Laboratories prepared and supplied the capsules with a sealed code.

TABLE 1.—*Age of Patients in Four Groups (Phase II Study)*

Drug Group	*Per Cent of Group* Over 50 Years	*Per Cent of Group* Over 70 Years
A	92%	17%
B	78	22
C	91	39
D	86	43

patient as a palliative procedure. Palliative resections carried out in patients with far advanced carcinoma were also evenly distributed among the groups. Each group also included several patients in whom peritoneal contamination was already present at the time of operation. In four patients, the colon was not opened at the time of operation. In one of these patients, disseminated adenocarcinoma was encountered and the procedure was limited to a biopsy. In the other three patients there was primary disease of adjacent organs in which involvement of the colon could not be excluded preoperatively.

Results

Side Effects. The incidence of side effects such as nausea, vomiting, abdominal pain or diarrhea was negligible. In no instance was it necessary to discontinue the drug for these reasons. There were also no significant differences apparent between the various agents and dosages used in Phase I and Phase II.

Condition of the Bowel. The mechanical cleansing of the bowel by the regimen used in this study was considered satisfactory in all cases.

Postoperative Infections. The postoperative infections encountered in the Phase I study are shown in Table 2. Although the number of patients in each group is small, it is interesting that the lowest incidence of postoperative infections related to the surgical procedure occurred in the patients receiving a placebo. Staphylococcal enterocolitis developed postoperatively in four patients, all of whom had received antibiotics before operation.

Wound and peritoneal infections encountered in the Phase II study are shown in Table 3. Although it has not been determined which groups received antibiotics or placebo, it can be seen that no possible combination of any two of the four groups would show a statistically significant difference.

Mortality. The deaths occurring in the two studies are shown in Tables 4 and 5. If one postulated that the patients in Groups A and C received the same agent, then the ratio of deaths due to infection in the placebo versus kanamycin group could be four to two (or two to four). Considering the number of patients in the study, this difference is not statistically significant. On the other hand, if the patients in Groups A and B or Groups A and D received the same agent, then the number of deaths resulting from infections would be equal in the placebo and antibiotic groups. In the Phase II Group, three additional deaths occurred which were not related to infection: One patient with cirrhosis of the liver died of massive hemorrhage from esophageal varices; another died of multiple pulmonary emboli, and the third of metastatic disease. Seven of the eight deaths occurred in patients with malignant disease. Three of these patients had distant metastatic lesions at the time of death.

Discussion

In the numerous reports which have appeared in the literature concerning the effectiveness of antibiotics and chemotherapeutic agents in reducing postoperative morbidity and mortality associated with operations on the rectum and colon, the conclusions have rarely been supported by well controlled studies comparing treated and untreated patients. The present study was carried out in a way to minimize bias in the analysis of the results.

Although each of the five drug groups in the Phase I Study was relatively small in size, it is interesting to note that the incidence of infections

TABLE 2.—*Incidence of Infections Related to Operation (Phase I Study)*

Drug	*Each Capsule**	*Number of Operations*	*Wound Infections*	*Perineal Infections*	*Peritoneal Infections*	*Enterocolitis*
Neomycin	500 mg	18	4	2	0	1
Kanamycin	500 mg	20	7	2	0	1
Neomycin	350 mg	18	2	3	2	2
Kanamycin	350 mg	19	7	3	0	0
Placebo		17	2	0	2	0

*Dosage was begun 72 hours before operation on schedule of two capsules every hour for four hours, then two capsules every six hours until the midnight before operation.

TABLE 3.—*Incidence of Peritoneal and Wound Infections by Group* (Phase II Study)*

Group	*No. Treated*	*Total Infections*	*Peritoneal Infections*	*Wound Infections*
A	24	9	2	7†
B	23	7	2	5†
C	23	6	2	4
D	21	8	3	5

*Grouped according to four different coded preoperative preparations.

†Infection limited to drain site in one patient in each of these two groups.

TABLE 4.—*Death in Each Drug Group (Phase I Study)*

Drug	*Each Capsule‡*	*Total Patients*	*Total Deaths*	*Deaths Related to Infection*
Neomycin	500 mg	20	1	1*
Kanamycin	500 mg	20	0	0
Neomycin	350 mg	20	2	1
Kanamycin	350 mg	19	2	0
Placebo		19	5	2†

*Infected before operation.

†One of these patients had a "pull-through" operation with probable impairment of blood supply; second patient had perforation of colon due to carcinoma and was infected prior to operation.

‡Dosage was begun 72 hours before operation on schedule of two capsules every hour for four hours, then two capsules every six hours until the midnight before operation.

TABLE 5.—*Deaths in Each Group* (Phase II Study)*

Group	*Total Patients*	*Total Deaths*	*Deaths due to Infection*
A	24	2	1
B	23	3	2
C	23	1	1
D	21	3	2
Total	91	9	6

*Grouped according to four different coded preoperative preparations.

related to operation was the lowest in the group receiving the placebo. In this placebo group, Staphylococcus aureus was never recovered from cultures of stool or of exudate from infections related to operation. No discernible differences in effectiveness were found between the two antibiotics or between the two dosage regimens employed.

Although the code has not yet been broken in the Phase II Study, some pertinent observations can be made. Considering only the criteria of mortality and the incidence of postoperative wound and peritoneal infections, there is no apparent significant difference between patients receiving kanamycin and those receiving a placebo. However, this is only a preliminary report and it does not include an analysis of other infections occurring in this group such as pneumonitis and urinary tract infections. Subsequent analysis and correlation of bacteriological data will be reported later.

The advisability of the routine use of antibiotics in preoperative preparation of the colon has previously been questioned by Tyson and Spaulding as well as by other investigators.[6,7,9] Although no definite conclusions can be reached in the present study as yet, our experience also raises doubt as to the necessity or desirability of routine preoperative "sterilization" of the bowel.

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Use of 5-IODO-2′-Deoxyuridine (Idoxuridine) in Cutaneous Herpes Simplex

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■ *Twelve patients with cutaneous herpes simplex were treated in a double blind series with either 0.1 per cent idoxuridine solution or a placebo. There was no significant difference in healing time between those receiving the drug and those the placebo. The same conclusion was noted in a series of eleven patients using either 1 per cent idoxuridine in a cream or a placebo.*

THE THERAPEUTIC efficacy of 5-iodo-2′-deoxyuridine (idoxuridine) in ocular herpes simplex infection appears established. That it is also effective in cutaneous lesions has been suggested but not confirmed.[1,2] Hence a study was made to resolve the question.

Two studies were performed. Idoxuridine in solution was used on one group of 12 patients with cutaneous lesions of herpes simplex; and in a group of 11 patients with similar lesions, 1 per cent idoxuridine in non-ionic base cream was used. Both compounds were administered in a random double-blind fashion with placebo controls. The idoxuridine solution contained 15 mg of idoxuridine in 15 ml of sodium chloride and distilled water with 0.5 per cent chlorobutanol. All preparations were used topically, four times daily, without dressings.

With the exception of one case of herpes simplex of the upper lip that cleared in two days, no significant difference in time of resolution was noted between patients using idoxuridine solution and those receiving the placebo, nor was there significant difference in the group using cream or a placebo. These results agree with those reported by Burnett and Katz[2] and by Ive.[5] However, in series reported upon by Hall-Smith, Corrigan and Gilkes[3] and Schofield,[7] results associated with idoxuridine were more encouraging. Perhaps the best method of application of idoxuridine, the most effective concentration and the ideal frequency of application are still to be determined.

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Congenital Chromosomal Syndromes

A Model for Pathogenesis

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■ *The origin of anomalies in the chromosomal syndromes is believed to be both polyetiologic and polypathogenetic. Whereas some malformations quite clearly appear to result from single gene mutations or from genic imbalance due to individual monosomic or trisomic loci, other anomalies (singly or in complex patterns) are better interpreted as originating from disturbances in particular biochemical pathways which affect the development of a variety of traits.*

Additional phenogenetic studies and the use of sophisticated biochemical analysis in persons with complex patterns of anomalies should provide a truer understanding of disease mechanisms and provide guidance for future studies which are aimed at the treatment and prevention of these intriguing misadventures of Nature.

THE G_1(group 21-22) trisomy syndrome (mongolism) and the D_1-(group 13-15) and E_1-(group 16-18) trisomics exhibit a remarkable variation in the number, pattern and severity of congenital malformations, with very few anomalies being constant. Nonetheless, in the majority of cases it is possible to establish the correct diagnosis clinically.

The malformations are generally believed to originate from the genic imbalance produced by triplicated genes (trisomic loci). Patau and coworkers[13] analyzed the phenotypic characteristics of patients with simple and partial trisomy of chromosomes 18 and D_1 and constructed provisional maps of the trisomic loci.[13] These investigators expressed confidence that "at least some of the main anomalies represent individual trisomy loci and that, by and large, the maps show their true sequence." And in conclusion, they indicated that "the diagnosis of 18 trisomy does not any more require a cytological confirmation."

Phenotypic variability in the chromosomal syndromes, according to Townes and coworkers[21] could be "readily attributed to the innumerable different combination of genes that are possible in a single individual trisomic for a given chromosome."[21] Although others had ascribed this variability to the genetical consequences of "relative homogeneity"[1] and "minimal crossingover,"[6] these conjectures were all based on the assumption that genetic variation of mutation origin was responsible for the many different patterns of anomalies.

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Mutagenesis and Genic Regulation

It is possible to make one clear distinction between the type of mutation that characterizes the chromosomal syndromes and that which typifies the molecular (genic) disorders. In the latter, intragenic aberrations (point mutations) arise from specific *qualitative* changes (base alterations) in desoxyribonucleic acid, while the chromosomal syndromes arise from *quantitative* changes (trisomy or monosomy of genic loci) in otherwise normal desoxyribonucleic acid.[16] Genic mutation in the chromosomal syndromes, while having been proposed by other investigators to account for the phenotypic variableness, probably does not play an essential role, but merely provides variety. Although it is entirely possible that the etiologic disturbances which lead to chromosomal aberrations also act to produce multiple genic mutations, possibly at loci with particular susceptibilities, the usual absence of anomalies in the genetically balanced translocates is evidence that genic mutations are incidental.

Jacob and Monod[5] demonstrated that some structural genes (in certain organisms) appeared to be regulated by *operator* loci. They offered the hypothesis that *operons* (*operator* and structural gene loci) were subject to induction and repression through a composite interaction of *regulator* genes with particular inducer (substrate) and repressor (product) substances. A modification of that hypothesis provides a satisfactory explanation for pathogenesis in certain molecular disorders in man and it has seemed applicable also to the origination of malformations in the chromosomal syndromes.[16,19] Extending their hypothesis to the trisomy syndromes, several investigators have explicated a mechanism to account for the persistence of fetal hemoglobin synthesis in older children with the D_1 trisomy syndrome (see Chart 1).[4,14]

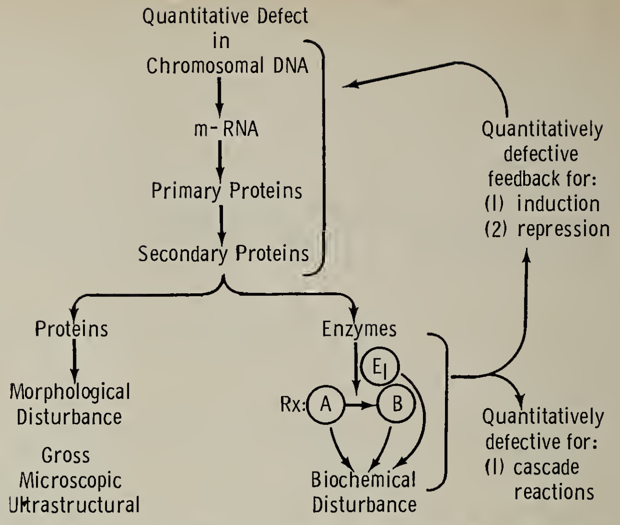

Chart 1.—Proposed model for the origin of malformations in the chromosomal syndromes when trisomic or monosomic loci are responsible. Biochemical disturbances may result from a quantitative change in substrate(A), product(B), or reaction enzyme(E_1). Feedback regulation is deficient because of genic imbalance produced by trisomy or monosomy of loci. Normal cascade regulation of nonallelic genes may also be disrupted.

Provocative Observations

Despite any general attractiveness of the foregoing interpretations of pathogenesis in the chromosomal syndromes, certain observations have been made which justify the consideration of alternative or additional mechanisms for the production of congenital malformations. In the case of the chromosomal syndromes, presenting as they do with rather complex patterns of anomalies, it is not surprising that skepticism was expressed when cytogenetic studies of patients with representative clinical features showed normal chromosomes. Patau and coworkers[13] indicated they had "encountered patients with complex patterns of anomalies that resembled the one or the other of the two new trisomy syndromes so closely that any interpretation not involving a common etiology appeared far fetched." Many of their patients did not have microscopically visible chromosomal abnormalities but the investigators had assumed that undetectable insertions or translocations were present.

Suffice to say, there is not general agreement with Patau and coworkers that their patients possessed undetected mosaicisms, hidden translocations or occult insertions. Representative clinical features which are characteristic of the various chromosomal syndromes have now been found in chromosomally normal persons with clinically apparent Klinefelter's syndrome,[15] Down's disease (mongolism),[2] Turner's syndrome,[3,15] and the E_1[12,15,20] and D_1[9] trisomy syndromes. It is of further interest to note that an infant with a group-A(2/3) translocation exhibited the regular anomalies of the E_1 syndrome,[7] an adolescent with a group-C(6/9) translocation presented with the usual features of mongolism,[18] and two children with proven E_1 trisomy had clinical features that were characteristic of the D_1 syndrome.[17] It goes without saying that one inherent difficulty in genetical studies is that of distinguishing between disorders which are closely alike. These disease mimics exist for both non-hereditary conditions (termed phenocopy) and genic mutants (termed genocopy). Deficiencies in plasma thromboplastin antecedent (PTA) and plasma thromboplastin component (PTC) are well known genocopies of antihemophilic globulin (AHG) deficiency hemophilia. Similarly, differentiation between idiopathic hypoparathyroidism, pseudohypoparathyroidism and Turner's syndrome is often difficult and the diagnosis may remain uncertain. One might appropriately ask whether or not children who are diagnosed clinically as having mongolism but who are chromosomally normal should be designated as mongols or be termed "pseudomongols.[18] Unless chromosomal aberrations are demonstrable, it seems worthwhile to distinguish the "pseudo-trisomy syndromes" from those in which chromosomal mutation can be observed, without de-emphasizing the phenotypic similarities.[19]

Analysis of the Anomaly Patterns

If the anomalies in the E_1 or D_1 trisomy syndromes are graphed according to their order of frequency, a rather continuous curve is obtained, and the various malformations occur with frequency values ranging from 1 to 100 per cent. In rare instances only has it been possible to correlate any of the congenital anomalies with those present in the parents, in siblings or in balanced translocates. There is no sound evidence that ordinary dominant or recessive genic mutations play a significant role in phenotypic development of the chromosomal syndromes. Many of the anomalies (short fingers, syndactyly, polydactyly, simian creases, harelip and ocular defects) do not show bilateral symmetry, an observation which has been generally interpreted as indicative of environmental influences.

Furthermore, when comparative analysis is made of the entire group of defects which have been reported in these autosomal trisomies (see Chart 2), the anomalies can be divided into seven major categories according to their occurrence in one or more of the syndromes. Some anomalies are encountered in all three syndromes, while others are either shared with another disorder or occur separately. The degree of overlap of these complex patterns of anomalies is sufficiently great that it must be seriously questioned whether or not there are individual trisomy loci for each of the anomalies in these three syndromes.

Model of Pathogenicity for Complex Anomaly Patterns

Rather than conclude that separate loci are present for the numerous anomalies in the complex malformation syndromes, it is suggested that certain malformations do not have their origin in mutation of separate genic loci, but instead arise somewhat indirectly because of aberrations in particular metabolic pathways which normally govern the expression of a great number of genes

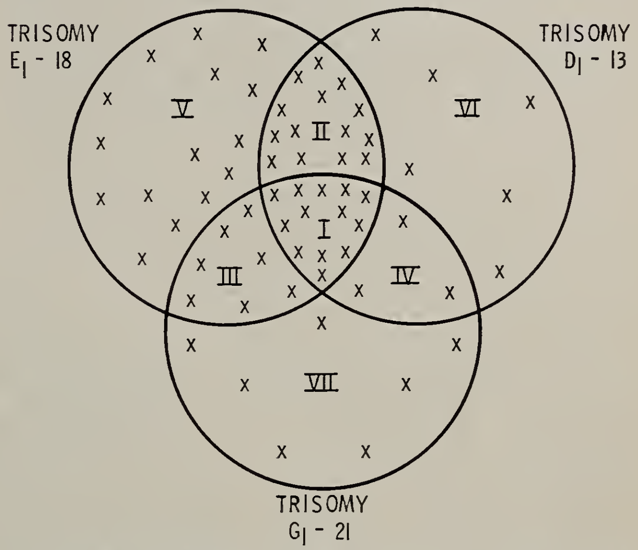

Chart 2.—Schematic representation of anomalies in the D_1-13, E_1-18, and G_1-21 trisomics, showing that some features are unique while others are variously distributed among the three syndromes. Roman numerals refer to anomalies possessing a particular distribution in these syndromes. Each cross(X) represents one of sixty-four different anomalies which have been recorded in these trisomics. Group I anomalies may be present in all three disorders, while those in groups II to IV are shared by two syndromes, and those in groups V to VII are unique to one particular syndrome.

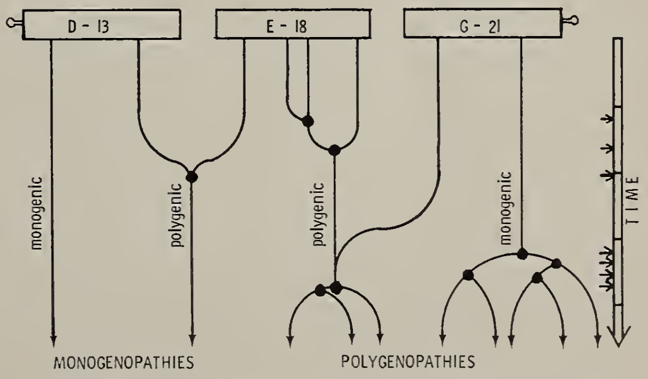

Chart 3.—Possible genic pathways of development for particular traits. Pathways may be controlled by single genes (monogenic) or multiple genes (polygenic). Aberration of a pathway can produce single anomalies (monogenopathy) or multiple anomalies (polygenopathy). Some of the pseudo-chromosomal syndromes may be monogenic polygenopathic conditions. A time scale denotes different times of gene activation and trait development.

which may reside not only on the trisomic or monosomic chromosome but elsewhere in the genome. Depending upon the number of chromosomal or genic loci affected, the pathways can be classified as monogenic (single gene) or polygenic (multiple genes); this is illustrated in Chart 3. The phenotypic expression of a pathway of either type may be monogenopathic (single trait) or polygenopathic (multiple traits). A variable degree of genic activity during different periods of embryogenesis would be possible if the polygenic pathways had several regulatory loci. Aberration of the metabolic pathways could arise from single genic mutations, genic imbalance due to trisomic or monosomic loci, antagonism or synergism of biochemical pathways governed by nonallelic genes or faulty supply and regulation of exogenously governed metabolites. It appears likely that an excess or deficiency of a single component essential to a complex metabolic pathway could invoke multiple malformations. These proposals could satisfactorily account for the sharing of complex patterns of anomalies by the different chromosomal syndromes and also explain their occurrence in cases which are chromosomally normal (pseudochromosomal syndromes).

In favor of the hypothesis are animal studies which have demonstrated the regularity with which certain vitamin deficient diets, vitamin antagonists, and other teratogens may produce more or less characteristic patterns of anomalies.[11] The similarities between these induced patterns of anomalies and those which are found in the chromosomal syndromes have been previously noted.[19] Additionally, discovery of a pathway alteration of the type required for this model of pathogenesis was recently described by McCoy and Chung.[10] They demonstrated a relative pyridoxine deficiency in nonpyridoxine supplemented women in pregnancy and a disposition for pyridoxal depletion in mongols. Their observation of a specific metabolic alteration in pregnancy provides support for the previous suggestion that phenotypic variability in the chromosomal syndromes may be governed by the flux of essential metabolites which control embryonic development.[16,19] The specific requirements for these regulatory metabolites (vitamins, hormones, enzymes and the like) will vary according to the stage of pregnancy, maternal nutritional status and the genetical composition of the mother and fetus. It is believed that the autosomal trisomy states impose particular metabolite deficiencies during the critical periods of embryogenesis.[16] Mongol children have also been shown to have a deficient excretion of 5-hydroxy indoleacetic acid, indol acetic acid and xanthuneric acid, both before and after tryptophane loading.[8]

It is reasonable to believe that additional metabolic disturbances will be found in pregnancy and in the new numerous chromosomal syndromes. It is further suggested that identical or analogous biochemical aberrations will be found to play causative roles in the pathogenesis of malformations in chromosomally normal persons having complex anomaly patterns. In constructing a model of pathogenesis based on the scheme in Chart 3, it is apparent that a minimum of four to seven metabolic "final common pathways" would be required in order to satisfy the hypothesis. However, as additional malformation syndromes are analyzed with respect to the trisomy syndromes, it is likely that upward to 10 or 20 different metabolic pathways could be subject to aberration. For example, the defects which are common to both the Turner XO and the E_1 syndromes might have origin from the same monogenic polygenopathy, and the similarities between the chromatin-negative and chromatin-positive cases of Klinefelter's syndromes could also result from a polygenopathic state.

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Psychological Aspects of Medical Prescription

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■ *Medication possesses a potential for therapeutic efficacy far beyond its chemical capacity if prescribed in ways which enlist patients' personality traits in a therapeutic direction. "Prescription" in this sense includes the physician's attitude (as the patient sees it) and subtleties in the way he fits his instructions to the kind of patient he is dealing with. This presentation deals with four kinds of patients—widely different in what they need from the physician—for whom some therapeutic "placebo" effect of prescription can be brought to bear:*

1. *Patients who are unduly fearful about what is wrong with them, and who look to the physician for calm sureness.*
2. *Systematic, controlled, organized patients, who like to share in their own medical management.*
3. *Patients who are excessively depressed about being sick.*
4. *Patients for whom "nothing works," but who can be helped by a physician who is willing to accept "failure" in dealing with them.*

For all of them, careful appraisal and sophisticated treatment are necessary.

IF AS MUCH EFFORT were made to enhance the "placebo effect" in clinical practice as is made to minimize it in research, subjective benefits from medication would be greatly increased. I am using the term *placebo effect* to designate the vector resultant of all the psychological factors entailed in the taking of medication. This includes the factors that reduce as well as those that enhance the basic chemical effects, and the factors in clinicians as well as those in patients.

The enthusiasm felt for a new drug is recognized as a reason for initial over-estimation of the value of such a drug. If this degree of enthusiasm could be maintained, subsequent use of the drug might be just as successful as the initial use had been. However, replication of initial studies by skeptical researchers usually indicates much less value in the drug, and this tends to dampen the enthusiasm of the clinical community. So it is inevitable that most medications will not produce therapeutic effects as much beyond their chemical capacity as it is theoretically possible for them to produce.

This being so, the attitude of clinicians toward the drugs they use is controlled in large measure

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by the current state of medical knowledge and opinion. It is therefore more useful to turn to factors within patients which affect the results of medication.

General Principles

Physicians generally recognize that their patients do not unfailingly have prescriptions filled and do not always take medicines as they have been instructed to do. Experience has taught that it is well to ask explicitly whether and how the patient is taking prescribed drugs and to deal with the causes of his failure to do so.

Factors related to medication reveal themselves during the taking of the history and in subsequent contacts with the patient. All people have certain attitudes toward drugs in general and other attitudes toward certain kinds of drugs. If such attitudes are not mentioned spontaneously, they come to light during discussion of previous illnesses and medications which have been self-prescribed or professionally administered in the past. Patients who share the common belief that oral medications are generally weak while injectables are potent will usually indicate this, along with prejudices about liquid versus tablet forms of medication. More importantly, patients may reveal that they equate the taking of medications with weakness and "pampering." They may "react badly" to almost all drugs. Or they may have always needed larger than average doses (or smaller than average doses) of any medications prescribed. This list could be expanded considerably.

If the patient recounts, with some degree of pride, that all the medications that others have prescribed for him have failed to do any good whatsoever, it is a naive physician who writes out a prescription for a new drug without dealing with the underlying mental set of the patient. If the patient has always had "bad reactions" to normal doses of medications, the experienced physician will not only begin with a drug in smaller than normal doses; he will also tell the patient that he has done so. If the medication to be prescribed is one that looks like a previously tried and ineffective one, it is well to let the patient know they are not the same.

The number of individual problems possible around the taking of medication is tremendous. Most problems are soluble by means of ordinary medical judgment—provided the physician recognizes that they exist.

Particular Kinds of Patients

Apart from general attitudes, the nature of a patient's personality should be taken into consideration in prescribing medication. But such considerations often require more than average sophistication. It is generally known, for instance, that patients whose personality is of the "hysterical" type are suggestible. Physicians may, therefore, tend to prescribe medication for such patients with especial efforts to suggest that it will be effective. However the medication may be a dismal failure, in spite of the attempt at suggestion. The suggestible patient tends to react to the physician's attitude as the patient perceives it from many kinds of clues, not just from reassuring or encouraging words. Thus, an underlying doubt about the probable usefulness of the medication may be reflected by an inadvertent facial expression; in such a case, the *real* suggestion may have been that the medication would *not* work. Because the physician may be unable to control his non-verbal expression of expectation and attitude, as well as for other reasons, mere verbal reassurance is often useless in suggesting anything. Hence, in the following discussion of particular types of patients, if it is noted that a particular attitude will be helpful, this should be taken to mean that the attitude will be helpful if it is *truly* held by the physician, not just if he *pretends* that he holds it.

The Anxious Patient

The term *anxious* is meant to denote patients who are unduly fearful about what is wrong with them, not necessarily patients who have a specific neurotic anxiety reaction. Such patients do best with a physician who is himself calm. Anxiety tends to be infectious; so, in such patients, is uncertainty. This is not meant to recommend a pretense of knowledge as to what is wrong and what should be done. But the anxious patient will respond well to the physician's confidence that he will ultimately be able to help the patient. I do not intend to recommend a casual or superficial history-taking or examination. On the contrary, with the anxious patient, the more thorough these are, the better. However, the casual attitude will have a reassuring effect *after* the thorough evaluation. Since the anxious patient tends to be preoccupied with his state of health, he will generally be frightened by detailed descriptions of what may be wrong, what is to be done and what may complicate treatment. For such patients, the simpler the information the more reassuring it will be.

The more complex the information, the more there will be to be worried about, and the worry may well aggravate the primary illness.

With such patients the same principles apply to prescription of medicines. The therapeutic effects and any prominent side-effects may be mentioned briefly and simply but should not be described in detail. If several medications may have to be tried, the patient should be told this at the outset to prevent increased anxiety if the first medication is not effective enough. For the anxious patient, it is often well, if the nature of the illness and the medication permit, to allow some leeway in dosage. The anxious person tends to feel in a state of entrapment, and his anxiety is increased by anything that implies "there is no way out." In the case of medication, the possibility of an extra dose represents a "way out." Since one facet of entrapment is unobtainability of something that is needed, the physician will do well to emphasize that he is available to the patient, in person or by phone, in case of need. The more available the physician is felt to be, the less likely the anxious patient is to call him.

The Compulsive Patient

The term *compulsive* is meant to designate the particularly systematic, controlled, organized patient, not necessarily the patient with obsessive-compulsive neurotic symptoms. Such patients require management almost opposite to that recommended for the anxious patient. The more detailed and organized the information that the physician gives them about their illnesses and medications, the better they do. For such patients, it is often best that they know the name of the medication and a reasonable amount of detail of its expected effects and side-effects. If the patient asks questions about safety, chemical features or relationship to other medications, the physician will do well to answer in as much detail as is appropriate to the patient's capacity to understand technical information. The schedule of dosage should be well organized and specific. With such patients, a drug should be taken "before meals" or "after meals" rather than "around mealtimes."

However, it should also be kept in mind that "control" is an important area for such patients. They may feel that taking medication represents "being controlled." Even so, a patient of this order may do well on medication if the physician can find a way of giving him some share in management of the medicinal regimen. This assignment of responsibility to the patient may be in the nature of permitting him to participate in decisions about dosage and schedule. If such decisions are to be shared by the patient, the basis for them should be laid down specifically in terms of symptoms or signs which are to guide his decision.

The compulsive patient does not need to have a physician who manifests the kind of certainty that was described as desirable for the anxious patient. He may do even better with a physician who manifests doubt, provided the physician has an organized, systematic, way of going about investigating the unknowns. The kind of calm certainty which reassures the anxious patient may suggest to the compulsive patient that the physician is a careless person who may be ignoring serious and dangerous matters in connection with his health.

The Depressed Patient

As with the other terms used, *depressed* is not meant necessarily to imply clinical depressive illness, but rather an excessive degree of depressive feeling about being sick. Seemingly paradoxically, one warning of possible depressive reaction to illness is an excessively minimizing attitude toward it. The potentially depressed patient may be so threatened by his underlying depression that he attempts to minimize his illnesses. The management of such a patient is most difficult. One form of minimization is neglecting to take prescribed medication. To force an awareness of the severity of his illness on the patient may precipitate a severe depressive reaction. Ignoring the minimization permits the patient to ignore the medication. The physician must walk a fine line in such cases. It is best if the patient can accept the fact of the illness in gradual degrees. One way to do this is by an insistence on the importance of the medication or other prescribed treatment procedures. It is often helpful here to enlist responsible family members in enforcing the treatment regimen.

For the frankly depressed patient, the management approach is less difficult, apart from the need to be alert for serious frank depressive *illness*. If this seems to be threatening, it is urgent to assess the suicide risk. Unless the physician is experienced in making such assessments, psychiatric consultation is desirable.

As physicians with experience in managing depressed patients have learned, it is most important not to minimize their depression. Family, friends or less sophisticated professional practitioners often try to cheer up depressed patients by telling them there is very little wrong with them. This tends to aggravate depressive reactions rather than to alleviate them.

Depressed patients do better with physicians who accept their view of themselves as ill, and who recognize the problem which being ill constitutes for the patient. The physician may (and, indeed, generally should) reassure the patient that he will eventually recover, if this is the case. But he should not minimize the present existence of the depressed feeling as part of the reassurance about the future. Medications should be prescribed with precision, much as for the compulsive sort of patient. However, with the depressed patient, control of the regimen should remain with the physician. The depressed patient is burdened by responsibility and should not have the burden aggravated by being asked to share in the responsibility for treatment. The expected effects and possible side-effects of medication may be conveyed to the patient, but, as with the anxious patient, this information should not be unduly detailed.

It is also important to warn depressed patients that the medication will probably take some little time to be effective. The more depressed a patient is, the more likely he is to underestimate the degree of objective improvement he undergoes in treatment. Thus he may appear to others to be improving without his recognizing this himself. To tell a depressed patient he is improving when he himself cannot recognize the improvement has the same effect as does minimizing his illness originally: It aggravates the depressive element.

It is well to caution overenthusiastic family members not to minimize the seriousness of either the primary physical illness or the depressive element. Otherwise they may be undoing at home what the physician is trying to accomplish in his treatment program. If there is a question of potential suicide, it is well to entrust the physical custody of the medication to a relative and not to the patient.

The Patient for Whom Nothing Works

There is a particular kind of patient who needs to be considered separately. Every practicing physician has had a number like him. This is the patient for whom nothing works. He tends to go from physician to physician, receiving from each a series of medications. All are, as have been all preceding, utter failures. Such patients are often the targets of medical wrath for their intransigence. Psychiatrists see such patients at times. They may have the satisfaction of affixing a codable term to the patient's illness, but they are most often equally unable to cure it. These patients are sometimes called "hypochondriacs" and sometimes "intractable" and sometimes by other names. Their shibboleth is that the history reveals multiple failures in attempted treatment of a symptom or symptoms. They are treatable within certain limits—by physicians who are willing to "fail" in order to succeed. These are patients who, for varying reasons and in varying ways, must remain ill in spite of treatment. Thus, the treatment will "fail" in the sense that it will not make the patient symptom-free. However, such patients do not "enjoy" their illnesses in any conscious way. Psychiatrists who speak of the enjoyment of illness (or of other distressing situations) mean only that there is a need for the unpleasant state which outweighs its unpleasantness. Any "enjoyment" of the unpleasantness is quite outside the patient's awareness. In many such cases, if not in most, the symptoms represent a way of maintaining some sort of interpersonal relationships which (in the patient's mind) depend on his being sick. Among others, the relationship with the physician himself can be an important one for such patients.

The successful physician with such patients is the one who can permit the patient to retain his symptoms, while continuing to treat him. "Treatment" here means maintaining the physician-patient relationship as one within which the patient can seek help and obtain emotional support without having to be "well." Physicians tend to hope for symptom-relief in their patients, but for the "intractable patient" this expectation is unreasonable. The physician must not come to look upon the patient as a "bad" patient just because he remains ill. Once the demand for symptom relief is abandoned, it is surprising how easy it is to treat such patients.

There are several elements to treatment of patients of this kind. First there is the physician's mental set, as noted above. Once it is assumed by the physician, it will be communicated to the patient without having to be put into so many words. Other things follow from this. When medication is prescribed, it need not be presented as something that will make the patient well, but as something that "may help" or as something that is "worth trying." There need be no implication that failure of the medication equals non-cooperation by the patient. A trial of several medications may be helpful. Although it may be necessary that no medication be effective in cure, it may be quite possible for the patient to accept one as more helpful than others. If maximum relief of symptoms has been achieved, there should be some consensus of satisfaction with the result by physician and patient.

In the foregoing discussion there is implication that medications will be used, but that is not to say that they should be used just for the sake of prescribing something. For some patients, it may be enough simply that the physician "follow" the patient's progress, listen to the course of his difficulties, and be alert to the possible development of organic disease which does require more active and specific treatment. It has been said before, but bears repeating, that hypochondriasis does not provide prophylaxis against organic diseases.

There are patients for whom medication may be advisable, even without organic indications for it. There are patients who can maintain a physician-patient relationship *only* around the prescription of medication. The physician need not be ashamed of using such an approach. On the other hand, such "placebo" medication should be prescribed when a careful evaluation of the situation indicates it is truly indicated, not just for the sake of something to do.

Warning

A paper such as this one is necessarily artificial, in that it discusses psychological traits as if they appeared in pure culture. This rarely happens in real life. Many patients have combinations of the factors discussed. A usually compulsive person may come to medical attention with a reaction of depression associated with a particular illness. A normally depressive kind of person may be in a state of anxiety related to the particular illness from which he is currently suffering. In cases such as these, the management should be addressed to the newer reaction that is superimposed upon the pervading one. Such newer psychological reactions more often represent a neurotic component of illness; and they are, for this reason, more disturbing and difficult for the patient to cope with. Medical management should be directed toward the approaches which are most therapeutic with regard to the neurotic decompensation. If the unfamiliar sort of emotional reaction subsides and is replaced by the more lifelong personality trait, the management may be altered to conform with the patient's dominant psychological state.

Other than for situations such as these, where a patient normally manifests a personality in which two elements are combined the physician must use his best judgment in blending the approaches suggested.

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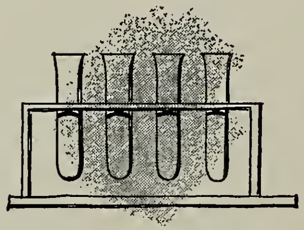

Roentgenologic Examination of the Small Bowel—*An Improved Technique*

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CHARLES R. FOX, M.D., *Walnut Creek*

■ *In examination of the small intestine, shortened transit time and improved quality were achieved by using the following items of regimen: 1, No laxative; 2, nothing by mouth for 8 hours before examination; 3, 600 ml of micropulverized barium sulfate; 4, patient to lie in right decubitus position for at least one hour between films; and 5, ingestion of 200 ml of cool tap water a half hour after the start of the examination.*

ROENTGENOLOGIC EXAMINATION of the small intestine may be a long procedure. Although many methods for accelerating it have been set forth, including the parenteral administration of neostigmine,[3] the oral administration of ice-cold saline solution and the use of purgatives,[2] we believe that such practices may introduce small bowel distention and disturbances of motility, which might confuse rather than clarify the diagnosis. Hence we have investigated another means of shortening the procedure without sacrificing quality of examination.

Material and Method

A variation of the optimal technique described by Nice[4] was used and was compared with our previous technique. Since a method was to be tested, patients with organic disease of the small bowel were excluded from this study. Two groups of patients were evaluated. *Group 1* (102 subjects) included all patients who underwent small bowel study in our department of radiology between June 1, 1962 and June 30, 1963. Patients in this group did not have colon preparation, took nothing by mouth after midnight preceding the examination, and received 300 to 500 ml barium sulfate USP at 8:00 a.m., the time of fluoroscopic study. Between the ingestion of barium and subsequent filming the patient sat in his dressing room or walked about. He took no food unless the examination required longer than four hours, in which case he received a light breakfast. *Group 2* (100 subjects) included all patients who underwent small bowel examination between July 1, 1963 and July 31, 1964. These patients also had no colon preparation and took nothing by mouth after midnight before the examination. At 8:00 a.m., each received 600 ml of micropulverized barium sulfate suspension. Between films, the patient lay in the right decubitus position for a half hour, then drank 200 ml of cool water, and again lay in the right decubitus position for a half hour.

The relative merits of the two techniques were judged on the basis of the following criteria:

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1. *Transit time*—from ingestion of barium to the first roentgenographic appearance of barium in the colon.

2. *Uniformity of filling*—a subjective impression of the total number of loops of small intestine satisfactorily opacified.

3. *Flocculation*—the formation of coarse collections of barium.

4. *Segmentation*—the formation of localized clumps of barium, within loops, not in conformity with barium in adjacent loops.

5. *Caliber of small bowel loops*—judged by the criteria of Caldwell and Floch[1]: That is, the diameter of the jejunum was considered abnormal if it exceeded 3.0 cm; that of the ileum was considered abnormal if it exceeded 2.5 cm.

6. *Mucous membrane pattern or clarity of bowel outline*—evaluated subjectively as optimal, coarse or fuzzy.

Results

The observations based on the above criteria are compared in Table 1.

The improvement in the average transit time, from 176 minutes for *Group 1* to 90 minutes for *Group 2,* is statistically significant. According to all criteria, the quality of the examination was also improved in *Group 2,* except for the incidence of abnormal intestinal caliber, where the slight difference in favor of *Group 1* was not statistically significant.

TABLE 1.—*Incidence of Undesirable Roentgenographic Qualities in Small Bowel Examinations*

Undesirable Roentgenographic Quality	*Incidence* *Group 1 (102 Patients)*	*Group 2 (100 Patients)*
Lack of uniformity in filling	4	2
Flocculation	31	15
Segmentation	37	11
Abnormal caliber	6	8
Poor mucous membrane pattern, or obscurity of bowel outline	14	5

Discussion

The different form of barium sulfate suspension used in *Group 2* accounts for the improvement in quality; but it is doubtful that the type of suspension *per se* would affect intestinal motility and, therefore, transit time. Shortening of transit time is thus traceable to differences introduced in other factors—positioning, quantity of barium used, and fluid intake. The technique described for *Group 2* is recommended to radiologists who want a safe, rapid, drugless method of examining the small intestine.

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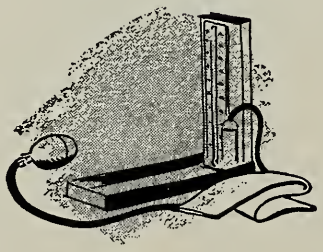

Muscle Paralysis in Herpes Zoster

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■ *Herpes zoster may, in some instances, cause motor paralysis as well as the usual sensory and cutaneous manifestations. It is suggested that the presence of electromyographic denervation potentials be used as the criterion of muscle paresis in order to avoid mistaking atrophy of disuse for true lower motor neuron disease. Use of the proper physical therapy procedures hastens the recovery of function and may serve to retard denervation atrophy and fibrosis in patients with muscle paralysis.*

HERPES ZOSTER, or shingles, is an acute infectious disease affecting man only. The causative agent is herpesvirus zosteri, a member of the herpesvirus group which all have an affinity for ectodermal tissues.[16] The morphologic and physical properties of the zoster virus are identical with those of the causative agent of chickenpox.[16] Epidemiological observations, serological studies and cultural characteristics also confirm the opinion of most virologists that the two diseases are caused by the same organism.[16,20]

The disease characteristically begins with itching followed by pain radiating into the distribution of a spinal or cranial sensory nerve. After a few days a vesicular rash appears in the cutaneous distribution of the sensory portion of the involved spinal root. At this point, the diagnosis becomes apparent from the peculiar combination of pain and eruption localized to a single dermatome or to adjacent dermatomes. Some variations may occur—for example, the eruption may precede the pain or pain may not occur or there may be signs of meningeal irritation. In most cases the pain subsides and the eruption heals, leaving a slightly pigmented scar. The total course of the illness is about five to eight weeks. The most common complications are secondary infection in the skin and persistent post-herpetic pain.[4,6,16] Correlating with the clinical manifestations, it has been shown that the virus can be recovered from a skin lesion and can cause an inflammatory reaction in the sensory ganglion, dorsal root and posterior horn of the spinal cord.[16]

There are rare cases of herpes zoster that do not fit the typical features and in which widespread involvement shows that the disease can be a generalized infection of the central and peripheral nervous system.[13] As examples, flaccid muscle paralysis can occur* due to spread of the infection from the posterior horn of the spinal cord to the

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*Reference Nos. 1, 3, 5, 8, 11, 19.

anterior horn and the motor nerve root.[1,8] Lower extremity spastic paralysis can be caused by interruption of pyramidal tracts in the spinal cord.[11,13] Cranial nerve involvement may cause paralysis of extra-ocular muscles[4] or facial paralysis as in the Ramsay Hunt syndrome.[5,10,18] Diaphragmatic paralysis can occur when cervical nerve roots are involved.[9,14] Upper motor neuron signs together with disturbances of consciousness can signify encephalitic involvement.[17]

It is these unusual types of herpes zoster, in which the motor system is involved, that come to the attention of the physiatrist, orthopedist, neurologist or other physician specializing in musculoskeletal disorders. We have recently had three patients with such cases under our care, and in addition we reviewed the records of ten other cases at the Los Angeles Veterans Administration Hospital.

Reports of Cases

CASE 1. The patient, an 89-year-old Caucasian man, a Spanish-American War veteran, living in Southern California, was in good health until mid-August 1964, when pain developed in the right thigh and was followed by a vesicular rash. A diagnosis of herpes zoster was made by his physician. The pain continued and the patient complained of poor appetite dating from the onset of the disease. About two weeks after the pain and rash appeared, weakness of the right lower extremity began, and gradually progressed to the point where the knee would buckle on ambulation. Five weeks after the disease began, the patient was admitted to the Veterans Administration Hospital because he was unable to walk. He also complained of persistent and severe pain localized to the medial side of the right knee.

About a year before admission, the patient had a transient episode of right facial weakness, lasting one day, which was felt to be unrelated to his present disease. There had been no recent injuries. The patient was under treatment for conjunctivitis for the preceding six months and had been receiving digoxin. He did not remember having had varicella and did not know of any recent contacts with it.

On examination, light brown scars of herpetic eruption were present in two strips on the right buttock and on the right anteromedial thigh. (See Figure 1.) Musculature of the right thigh, particularly the vastus medialis, appeared atrophied but the legs were of equal circumference at the thighs and calves. Pronounced weakness in the right lower extremity was found on manual testing of the muscles, the proximal muscles being weaker than the distal. Specific muscle group ratings were as follows: hip flexors, poor; hip adductors, fair; hip abductors, fair; quadriceps femoris, poor; foot dorsiflexors, good; foot plantarflexors, good. Deep

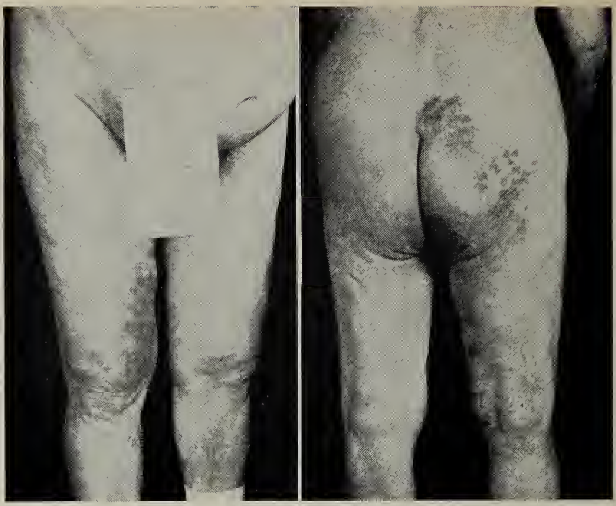

Figure 1 (Case 1).—Photographs showing the distribution of healing vesicular rash about six weeks after onset of disease.

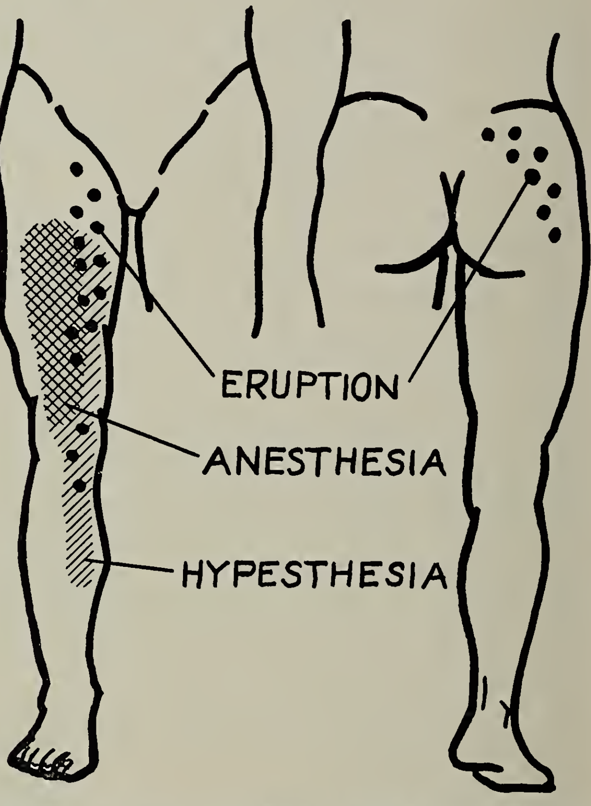

Figure 2 (Case 1).—Diagram showing the distribution of sensory loss to pinprick in relation to the location of the eruption.

tendon reflexes were depressed equally in knees and ankles bilaterally. There was an area insensible to pinprick on the anterior aspect of the right thigh from mid-femur to the patella, and medially there was a larger area of decreased sensation (Figure 2). No impairment of sensation could be found in the buttock, the back of the leg or the foot. Electromyographic examination showed denervation potentials consisting of fibrillation and positive sharp waves in the quadriceps, anterior tibial, peroneus longus and gastrocnemius muscles. X-ray examination of the lumbosacral spine showed advanced degenerative changes with large vertebral osteophytes.

A physical therapy program was prescribed, consisting of range of motion exercises of the right lower extremity joints to prevent contractures, progressive resistance exercises to strengthen the weakened musculature and galvanic electrical stimulation to help preserve denervated muscle while awaiting regeneration of the involved nerves. After ambulation training the patient was able to walk with the help of a pick-up walker in spite of only a small increase in strength in the paretic limb. At no time requiring more than salicylates, the pain gradually subsided over approximately three months. About four months after the onset of the disease the patient was discharged to the care of relatives out of town. The final outcome of the paralysis was not ascertained.

CASE 2. A 44-year-old woman bookkeeper had at first an itching sensation over the right upper extremity and then severe pain and a vesicular rash over the distal arm, dorsal aspect of the forearm and the ulnar aspect of the hand in the area of dermatomes supplied from the seventh and eighth cervical nerves. Weakness of the triceps, ulnar wrist extensors, the extensor pollicis longus, opponens pollicis, the interosseus muscles and the ulnar-innervated lumbricals became evident as the rash began to subside. The patient was unable to write or to use her hand because of pain and weakness.

Electromyographic examination six weeks after the onset of the illness revealed fibrillation of denervation activity in the muscles of the right upper extremity supplied by the anterior primary ramus of the eighth cervical nerve root. The denervation activity was most pronounced, quantitatively, in the pure C8-innervated area (flexor carpi ulnaris, dorsal interossei and adductor pollicis muscles).

Treatment consisted of whirlpool ultrasound and neuromuscular reeducation techniques. Electrical stimulation was added a week later to retard denervation atrophy. Pain regressed slowly and limited function returned. It was believed that the patient would require a fairly long program of physical therapy for optimum functional recovery.

CASE 3. A 68-year-old housewife had first an itching sensation over the right ear and face and then a vesicular rash over the outer surface of the ear. Pain in the ear, the face, and the right side of the neck developed three days later along with obvious weakness of the right facial muscles.

On examination six weeks later, incomplete paralysis of the right facial musculature was noted. The eyelid could not be completely closed, the patient was unable to whistle and there was absence of spreading of the orbicularis oris muscle on the right side. Sensitivity of the skin over the external ear was also present. Electromyographic examination showed moderate, partial denervation of the right frontalis, nasalis and orbicularis oris muscles.

A diagnosis of herpes zoster involving the right facial nerve (Ramsay-Hunt syndrome) was made on the basis of the history, clinical findings and electromyographic examination.

Physical treatment, begun immediately, consisted of electrical stimulation, massage and resistive exercises. Progressive improvement in muscle strength has been evident.

Study of Case Records

Our interest aroused by these three cases and further stimulated by an excellent review of the records of cases at Massachusetts General Hospital by Grant and Rowe,[8] we undertook a review of the case histories of all patients at the Veterans Administration Hospital, Los Angeles, who had a diagnosis of herpes zoster during the period 1953-1964. In many of these cases the zoster was not the primary diagnosis, and often, with or without motor paralysis, it was an incidental finding and not carefully studied. None of these patients were seen by the authors and only chart notes were available for evaluating the cases.

There were 208 patients with a diagnosis of herpes zoster in this group. In ten cases there were sufficient findings recorded to make a reasonably certain diagnosis of motor paralysis due to the zoster. Unfortunately, electromyography was not

TABLE 1.—*Anatomic Location of Herpes Zoster in Cases Reviewed from Records of the Veterans Administration Hospital, Los Angeles, 1953-1964*

Location	*All Cases*	*Paralytic Cases*
Brain (encephalitis)	1	0
Scalp & Neck	7	0
Cranial Nerves	51	8
Upper Extremity	21	0
Trunk	91	1
Lower Extremity	30	1
Generalized	2	0
Unknown	5	0
	208	10

done in any of these cases for positive evidence of lower motor neuron disease. The age range of the patients was similar to that noted in previous reports.[8] The anatomic sites of the zoster infection are shown in Table 1. The table does not include the three cases with which the present report began. Brief summaries of the ten paralytic cases found in the histories studied are given below.

CASE 4. The patient was a 65-year-old Caucasian man with diabetes. A herpes zoster eruption developed over the left side of the face on the forehead, eyelid, cheek and nose. It had been present for four days when the patient was admitted to the hospital May 20, 1953. Conjunctivitis of the left eye was also present. Left upper lid ptosis, enophthalmus, and extra-ocular muscle paresis gradually developed. The patient was discharged five weeks later in an improved condition to be followed as an outpatient for unrelated conditions of arteriosclerotic chronic brain syndrome and peptic ulcer. Corneal keratitis developed in the left eye and four months later he was readmitted for tarsorrhaphy. The ocular movements at that time were believed to have returned to normal.

CASE 5. A 56-year-old Caucasian woman was examined by the ophthalmological consultant on January 5, 1955 and found to have left fourth cranial nerve paresis probably due to herpes zoster involving the skin about the eye. An eye patch for diplopia was recommended. No further information is available.

CASE 6. A 74-year-old Caucasian woman was admitted to the hospital October 15, 1958 with complaint of nocturnal radicular pain and blistering in the dermatomes on the right side supplied from the twelfth thoracic and first lumbar roots. This condition had been present for ten days. A diagnosis of herpes zoster was made. The skin lesions responded to local treatment and the patient was discharged in two days. On readmission two months later the examining physician noted that, with the patient standing, there was a slight bulging of the right side of the abdomen associated with decreased muscle tone. On retrospection he recalled that the bulging had been present on the earlier admission. The patient was advised to wear a corset. No further information is available. We interpreted these findings as indicative of abdominal muscle paresis probably due to the herpes zoster infection.

CASE 7. A 76-year-old Caucasian man noted onset of a rash and burning pain behind his right ear a week before he was admitted to the hospital February 17, 1959. On admission he had vesicular dermatitis on the right side of the neck, jaw, head and right ear. A week after admission, peripheral seventh cranial nerve paralysis appeared. This man had a three- to four-year history of arthritis of undetermined type for which he had been receiving steroids. While still in hospital for further examination and diagnosis related to arthritis, he was given electrical stimulation to the right face. About two months after admission bronchopneumonia developed and he died.

CASE 8. The patient, a 45-year-old Caucasian man, an addict to alcohol who had had left nephrectomy in 1946 for tuberculosis, was admitted to the hospital May 8, 1959 with pain and swelling in the right eye for one week followed by a vesicular eruption over the right side of the scalp, the forehead and nose. An ophthalmologist noted involvement of the right cornea. The lesions responded to local application of antibiotics, but slight ptosis of the right eyelid remained. When the patient was examined six months later the right pupil was smaller than the left and responded sluggishly to light. He also had post-herpetic neuralgia. In 1956 he had had a skull fracture for which left frontal craniotomy was done. Therefore, it is possible that the right lid ptosis and constricted pupil were due to the trauma rather than herpetic involvement of the third cranial nerve.

CASE 9. An 84-year-old Caucasian man entered the hospital September 23, 1959 with history of pain in the left side of the face followed in two weeks by blisters in the distribution of the ophthalmic division of the left fifth cranial nerve. On physical examination, ptosis of the left eyelid and a dilated left pupil which did not react to light were observed. About 10 days after admission a cerebrovascular accident with right hemiparesis occurred. Three weeks later the patient died of myocardial infarction.

CASE 10. A 75-year-old Caucasian woman entered the hospital August 7, 1961 with severe pain of a week's duration in the right ear, neck, face, teeth, throat and shoulder. A rash over the back of the right ear had started three days before admission and had spread over the right side of the face and head. Slight weakness of the facial muscles on the right side was noted on admission examination. The rash improved on local treatment and the pain subsided. The outcome of the right facial paresis was not recorded.

CASE 11. A 46-year-old Caucasian man entered the hospital October 12, 1961 acutely ill, with pain and swelling in the left pinna, left temporal headache, nausea, dizziness, fever up to 103°F and nightly chills for six days. Three days before admission, peripheral left facial nerve palsy had begun. An audiogram showed a mild air conduction loss in the left ear. A diagnosis of Ramsay Hunt syndrome (herpes zoster oticus) was made. Antibiotics were used topically to treat a secondary infection of the external auditory canal. Within a week the acute phase subsided and partial function returned in the facial musculature. Amblyopia on the left was not attributed to the zoster. Further information was not available.

CASE 12. A 52-year-old Filipino with systemic lupus erythematosus, was admitted March 7, 1962, a week after a rash developed on the right side of his face in the distribution of the ophthalmic division of the fifth cranial nerve. The lesion was different from the butterfly rash of lupus erythematosus. The herpetic rash involved the cornea and there was also iritis of the right eye. Some drooping of the right side of the mouth, which was of unknown significance, was noted on admission examination. The hospital course was complicated by an eruption, presumably due to chloroquine which was administered for the lupus, by pulmonary disease and by bilateral parotid gland atrophy. Persistent dilatation of the right pupil, noted on this and on subsequent admissions, was attributed to the zoster.

CASE 13. A 58-year-old Caucasian woman who had diabetes was admitted to the hospital March 18, 1964 with severe pain in the left leg and a herpes zoster eruption of two weeks' duration over the first and second sacral nerve root distribution. The onset of the disease was associated with cervical and back pain, headache, chills and fever. The left knee and ankle reflexes were absent. Muscle testing showed weakness of left ankle dorsiflexion and plantarflexion and weakness of extension and flexion of the left knee. Five weeks after admission the pain was slowly resolving and the patient was able to ambulate without crutches. Unfortunately, electromyography was not done to prove the presence of lower motor neuron disease. Long-term follow-up is not available.

Comments

Various investigators have suggested that motor paralysis might be a relatively common finding in herpes zoster.[7,8,9] Grant and Rowe[8] on searching the records of the Massachusetts General Hospital uncovered five definite cases of paralysis among 101 cases of herpes zoster. However, as they recognized, this probably does not represent a true incidence of paralysis. Burgeon and coworkers[5] pointed out that herpes zoster is relatively benign and not many persons who have it enter hospitals or even seek medical care. In their report on a series of 206 cases of herpes zoster from the dermatology and ophthalmology departments of the Hospital of the University of Pennsylvania and outpatient department of Childrens' Hospital of Philadelphia, there was only a single case of extra-ocular muscle paralysis. Taterka and O'Sullivan,[19] after searching the literature in 1943, could collect only 44 cases of motor paralysis in herpes zoster, and Grant and Rowe[8] in 1961 could find reports of only 42 cases of extremity paralysis. Extra-ocular muscle involvement associated with fifth nerve gasserian ganglion zoster and facial nerve paralysis in the Ramsay Hunt syndrome seem to be more common.[5,8] More generalized, severe central nervous system involvement appears relatively rarely.[12,13,15,17]

From our own review of cases of herpes zoster from the files of the Veterans Administration Hospital, Los Angeles, it appears that true lower motor neuron lesions are uncommon, particularly in the extremities. Weakness alone, or even absence of a deep tendon reflex should not be taken as conclusive evidence of motor involvement due to the zoster. We have found that pain alone may keep a patient from responding with his full strength to manual muscle testing. Even after resolution of the pain, considerable disuse atrophy of muscle with its associated weakness may remain for some time, giving a false impression of muscle paralysis. Absence of deep tendon reflex can be due entirely to sensory ganglion involvement. A suggestion is proposed, therefore, that electromyographic evidence of denervation be taken as the criteria of true motor paralysis. This should occur in a myotome reasonably closely associated in anatomic location with a region of typical pain and eruption of herpes zoster. Careful manual muscle testing and a neurological examination are invaluable, of course, in every case of zoster in order to disclose those in which paralysis can be suspected. Other findings of electrical testing, such as reaction of degeneration and failure to respond to faradic stimulation, are also diagnostic of true motor paralysis, but the electromyogram is more sensitive and reliable.

As in any neurological disease, the physical treatment of the patient is a most important factor. Broadbent (1866)[3] in presenting the first case of a paralytic extremity due to zoster to be recorded in modern medical literature, described the development of a "frozen shoulder" in the patient. This can be almost entirely prevented by suitable physical therapy, as was done, for example, in a more recent case reported by Parker and Ramos (1962).[14] In one of the cases herein reported (Case 1) an elderly, bedridden man was returned to ambulatory status in a walker mainly through training in the use of his remaining muscle power. The improvement in his physiological and psychological status and the improved prognosis for survival needs no elaboration. With regard to the muscle itself, galvanic electrical stimulation and massage are available to maintain the best possible condition while awaiting reinnervation. Pain may be lessened or abated by treatment with ultrasound administered over the involved dermatomes.

We have not been able to discover, either from the literature or from the cases herein reviewed, what the effect of drugs such as protamide, vitamin B_{12}, or steroids might be on the course of a motor paralysis due to herpes zoster.

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LYSOSOMES:
Some Pathologic Implications

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LYSOSOMES form a heterogeneous group of intracytoplasmic particles characterized by a single outer unit membrane, in contrast to the double membrane of mitochondria. The particles received their name from the concept that the liver cell contains a special group of organelles associated with lytic (hydrolytic) enzyme activity, but lacking enzymes of oxidative metabolism. A further feature of their enzymic equipment pertains to their low activity when existing in an unactivated state.

The lysosome concept, as originally proposed by de Duve and his colleagues[21,23] a decade ago, embodied biochemical evidence for the presence of a distinct class of intracytoplasmic particles in liver homogenates. The hypothesis emerged from studies on the acid phosphomonoesterase activity and other hydrolytic enzymes of rat liver. Subsequent work has extended the biochemical findings to other tissues, and morphological, histochemical and electron microscopic studies have identified an acid phosphatase-bearing particle of great heterogeneity.

While the major role of lysosomes in the economy of the cell is still speculative, morphologic and biochemical studies have suggested an involvement in cellular necrosis, involution and phagocytosis. It is proposed in this review to summarize the main biochemical and morphological characteristics of these particles.

Biochemical Indentification and Properties

The biochemical criteria for identification and characterization of lysosomes were originally obtained on rat liver homogenates. Recently, however, particles fulfilling most of these criteria have been studied in other tissues and while the presence of lysosomes in many tissues is suggested, critical evidence for the presence of lysosomes is really only available in a few instances (Table 1). Biochemically, however:

1. The particles possess a hydrolytic enzyme complement lacking enzymes of oxidation and transfer reactions.
2. The hydrolytic enzymes have optimum pH's in the acid range.
3. The enzymes are sedimentable in their unactivated state.
4. The particles exhibit structure-linked enzyme latency.
5. The particles are limited by a membrane.

These criteria make no mention of particle size, as electron micrographs of purified lysosomal pellets from rat liver[22] and cytochemical staining have indicated pronounced heterogeneity in shape and size.

Chart 1 shows the known enzymic complement of the hepatic lysosome and diagrammatically embodies morphologic and physiologic properties. The absolute as well as relative concentration of the acid hydrolases varies from tissue to tissue. The absence of one or more enzymes of the group has occasionally been noted in some tissues. For

TABLE 1.—*Tissues Containing Particles Fulfilling the Biochemical and Morphologic Criteria of the Lysosome*

Hepatic dense bodies (pericanalicular)[62]
Kidney droplets ("phagosomes")[56,74,75]
Polymorphonuclear granules[11,13]
Kupffer cells, alveolar and peritoneal macrophages[12,89]
Thymus "dense bodies"[68]
Neuronal dense body granules[63,83]

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example, C_3H mice are characterized by low levels of β-glucuronidase.[14,66] Some lysosomal particles may contain an enzyme not normally found in the lysosomes as a group; polymorphonuclear granules, for example, contain lysozyme and a nucleotidase.[11] Recent work has removed the uncertainty concerning the possible lysosomal localization of uricase, catalase and D-amino acid oxidase activity. These enzymes are now thought to be located in the hepatic microbody or "uricosome."[4,86]

It is important to remember that all acid hydrolases are not localized entirely within the lysosomes. β-glucuronidase shows partial association with the microsomal fraction[66]; acid phosphomonoesterase is also present in the soluble fraction and is here distinguished by its susceptibility to alloxan and lack of sensitivity to tartrate inhibition.[59,72] Also of note is that an artifactual proportion of the acid hydrolases may occur in the soluble phase due to variable degrees of mechanical resistance of the particle during the homogenization procedure. For instance, spleen particles are very sensitive to mechanical breakage,[15] while homogenates from lactating rat mammary gland contain a higher proportion of sedimentable acid hydrolase activity when prepared with an Emanuel homogenizer than when prepared with a Potter-Elvehjem homogenizer.[33]

Chart 1 suggests that the bounding membrane of the lysosomal particle confers structure-linked latency to the entrapped lysosomal enzymes. Morphologic and centrifugation evidence has demonstrated the roughly spherical nature of the lysosome but unequivocal evidence of a distinct limiting membrane is not seen in all instances. The biochemical evidence suggesting the sac-like representation of the lysosome was based upon the behavior of them as an osmotically dependent particle. Koenig,[46] has challenged this view, proposing that lysosomes are solid bodies in which various enzymes are retained by ionic bonding. The nature of the limiting membrane has been under investigation and current evidence suggests that it is of a lipoprotein nature,[5,24,50] normally impermeable to substrate and internal enzymes. Our observations with phospholipase C and the observations of other investigators suggest that this impermeability is only relative.[84]

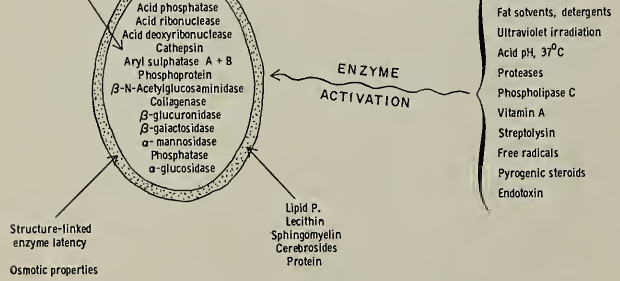
Periodic acid-Schiff positive
Ferritin
Metachromatic
Acid phosphatase
Acid ribonuclease
Acid deoxyribonuclease
Cathepsin
Aryl sulphatase A + B
Phosphoprotein
β-N-Acetylglucosaminidase
Collagenase
β-glucuronidase
β-galactosidase
α- mannosidase
Phosphatase
α-glucosidase
ENZYME
ACTIVATION
Physical agents
Fat solvents, detergents
Ultraviolet irradiation
Acid pH, 37°C
Proteases
Phospholipase C
Vitamin A
Streptolysin
Free radicals
Pyrogenic steroids
Endotoxin
Structure-linked enzyme latency
Osmotic properties
Lipid P.
Lecithin
Sphingomyelin
Cerebrosides
Protein

Chart 1.—The lysosome as a biochemical concept. Embodied information mainly derived from investigations on rat liver and summarized in reviews of de Duve[21,22]; Novikoff[60]; Shibko and Tappel[72,77]; and Weissmann.[92]

Tappel and coworkers[77] have prepared a purified liver lysosomal pellet in quantities which has enabled them to study some lysosomal properties *in vitro*. Chart 1 incorporates some of their data on lysosomal composition. These investigators demonstrated light-scattering by lysosmes in 0.25M sucrose solutions comparable to that seen in mitochondrial suspensions, suggestive of osmotic swelling. The presence of phospholipid and periodic acid-Schiff positive, diastase-resistant, metachromatic material, as indicated by staining procedures, is characteristic of liver and kidney particles.[18] Novikoff[60] and Koenig[47] pointed out that acid phosphatase-positive granules seen by light microscopy in proximal tubules of rat kidney correspond to the auto-fluorescent granules demonstrated in the kidney by Sjostrand.[73] Maunsbach suggests that acid phosphatase activity and auto-fluorescence are associated with the same granules in the proximal tubules.

Morphological Identification of The Lysosome

Gomori[32] introduced and improved the cytochemical staining technique for localization of acid phosphatase. This technique demonstrated the intracytoplasmic particulate nature of acid phosphatase and suggested, albeit weakly, that acid phosphatase may be located in association with an intracytoplasmic particle. Novikoff and coworkers,[62] in 1956, examined enriched acid phosphatase fractions, prepared by de Duve and his colleagues, in the electron microscope and demonstrated the presence of a number of distinctive particles suggestively identified with the dense peribiliary bodies (Figure 1) described by Palade and Siekevitz.[67] Lysosomes, largely freed from microbodies, mitochondria and fragments of endoplasmic reticulum have been prepared by means of density gradient centrifugation in highly purified pellets, and show the expected structure of the peribiliary dense body.[22] Moreover, the application of the Gomori acid phosphatase technique to liver and other tissues,[17,38] the electron microscopic study of subcellular fractions isolated by differential centrifugation from liver and kidney homogenates[52] and the examination of acid phosphatase preparations in the electron microscope[17,25,39] all have contributed important, detailed and unequivocal cytologic identification of the hepatic lysosome. Unfortunately, a definite correlation between morphologic and biochemical lines of evidence has only been obtained in a few tissues (Table 1), which underlines the problem in defining morphologically an essentially biochemical concept. Moreover, the morphologic studies have indicated the decidedly pleomorphic nature of the lysosome. Iron, in the form of ferritin, has been identified in liver and kidney lysosomes (siderosomes of Richter).[69]

In contrast to the mitochondria (Table 2), the lysosomes show pronounced cellular heterogeneity and individual polymorphism even in the same tissue. The fine structure of renal droplets contrasts with that of hepatic dense bodies and the specific granules of the polymorphonuclear leukocytes. Morever, early in the development of the lysosome concept, tissues undergoing physiological and pathological changes showed enlarged cytoplasmic bodies rich in acid phosphatase.[60,63] These were termed *cytolysosomes* and were postulated to be involved in a slow degradation of organelles within normal cells, since they were only occasionally seen in the liver and kidneys of normal animals.

A Unified Concept of Lysosomal Function

Proposed Genesis of Lysosomal Enzymes and Origin of Particles. A most critical problem is the origin of the hydrolases found in the lysosomal particles. The association of ribose nucleoprotein particles and the endoplasmic reticulum is well known in the synthesis of protein and enzymes. Van Lancker provided evidence that acid phosphatase and β-glucuronidase activity increases in the microsomal fraction after partial hepatectomy; and kinetic, temperature inactivation and isotopic labeling studies demonstrated that the β-glucuronidase found in the lysosome is synthesized in the endoplasmic reticulum. The electron microscope has demonstrated close association between the smooth endoplasmic reticulum in the Golgi zone and the endoplasmic reticulum. It will be remembered that the Golgi apparatus consists of parallel, flattened sacs and numerous small vesicles and

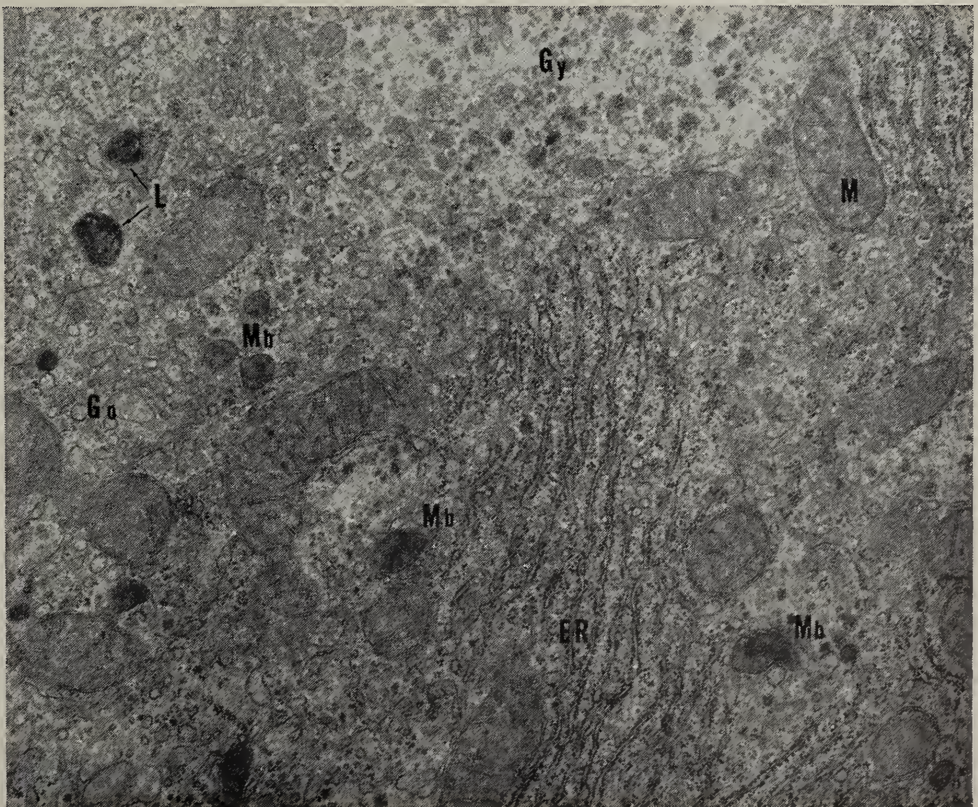

Figure 1.—Medium power electron micrograph showing portion of hepatic cell cytoplasm. Many ribosomes are dispersed throughout the cytoplasm, most of which are attached to the endoplasmic reticulum (ER). The Golgi zone (Go) appears as a smooth-surfaced, membranous, vesicular and vacuolar system, focally in continuity with the endoplasmic reticulum. Glycogen granules (Gy) are easily identified, occurring in clusters with a diameter slightly greater than the adjacent ribosomes. Oval and round mitochondria (M) containing inner membranes, and rare granules are interspersed with the smaller lysosomes (L) and microbodies (Mb). (Epon. Lead hydroxide ×20,000.)

TABLE 2.—*Morphologic and Biochemical Features Differentiating the Major Cytoplasmic Organelles*

Characteristics	*Mitochondria*	*Microbodies*	*Lysosomes*	*Cytolysosomes*
Size	0.6-1.3 μ	∼ 0.7 μ	Pleomorphic 0.5 μ (0.5—1.5)	> 1.5 μ
Shape	Oval filamentous	Round	Round	Irregularly spherical
Limiting membrane	Triple	Single	Single	Variable
Matrix density	Finely granular	Medium density	Dense Granular Peripheral "halo"	Dense Granular Inclusion material
Internal structure	Cristae Dense particles	Internal lamellated body ("nucleoid")	Polymorphic Vacuolation (ferritin)	Mitochondrial and ER debris "Myelin figures"
Enzyme complement	Cytochromes Flavoproteins Krebs' and fatty acid oxidation cycles	D-amino acid oxidase Uricase Catalase	See Fig. 1	Acid phosphatase
Staining histochemistry	Janus Green B Dehydrogenases	——	PAS positive Diastase resistant Metachromatic Autofluorescent Acid phosphatase β-glucuoronidase	Acid phosphatase

saccules approximately 25 to 50 mu in diameter. In secretory cells and neurons, larger dilated portions of the Golgi apparatus are present and referred to as Golgi vacuoles. It is suggested that mature lysosomal particles receive their hydrolases via the Golgi system. Kuff and Dalton[48] demonstrated a high concentration of acid phosphomonoesterase in the large Golgi membrane fraction. Although it is reasonable to assume that the primary lysosome is represented by a budding off of some portion of the Golgi apparatus, the true relationship of this postulated structure and intracellular autophagy, pinocytosis and phagocytosis is unknown.

It is thus reasonable to suppose that lysosomes are involved in processes of intracellular acid hydrolysis. It is a further feature of the concept that the segregation of the lysosomal hydrolases within relatively impermeable membrane structures is an essential component of the localization of lytic processes and the protection of the cell against generalized digestion. These phenomena are excellently exemplified in the digestion of foreign material, physiological phagocytosis, pinocytosis and probably in the localization of intracellular necrosis and involution of cells during their embryonic differentiation.

Chart 2 summarizes a concept of the genesis and physiologic role of the lysosome in the economy of the cell. The natural history of the lysosome has been arbitrarily divided into three phases, those of (a) vesiculation, (b) differentiation and (c) development. The phase of vesiculation is represented by the budding off of small vesicles and (postulated) saccules from the terminal segments of the Golgi apparatus. These vesicular buds are thought to contain the hydrolases manufactured and transported to the Golgi zone via the endoplasmic reticulum. The second phase, that of lysosomal differentiation, presupposes that the early or primary lysosomes may differentiate along four or more morphologic paths depending upon cellular species and the immediate needs of the cellular economy.

1. The formation of peribiliary dense bodies with and without vacuolation and small entrapped myelin figures, and/or ferritin granulation presumably passes through a more elementary phase in which myelin figures, vacuolation and ferritin deposition may be absent.

2. In the phenomenon of endophagy, comprising the related processes of phagocytosis, pinocytosis, phagosome formation and digestive vacuole formation, close cohesion of the endocytic vacuole and the primary lysosomal vacuole occurs with the formation of an intra-cellular digestive vacuole. Cohn, Hirsch and Wiener demonstrated the explosive liberation of polymorphonuclear neutrophilic

granule contents upon membrane fusion of the ingested vacuole and granules.[13,36]

3. In more highly specialized cells, the formation of storage granules containing digestive and lysosomal hydrolytic enzymes is observed as exemplified in the case of the polymorphonuclear leukocyte, eosinophil and also during the early formation of secretory granules in Paneth cells[7] and pancreatic acini. Of interest in this respect is the phenomenon of reversed pinocytosis where presumably a specialized particle containing hydrolytic enzymes may be formed and extruded through the limiting cellular plasma membrane as has been proposed in the case of osteoclastic activity. A somewhat related, albeit speculative, mechanism may exist in the quantal release of acetylcholine from synaptic vesicles upon fusion with the presynaptic membrane.[70]

4. The formation of cytolysosomes and autophagic vacuoles has been postulated in which isolated intracellular digestive events may occur.

The natural history of the lysosome suggests that some interconversion of the proposed lysosomal states may occur during development along any one postulated path. Moreover, the formation of residual intracytoplasmic bodies, as exemplified by lipofuscin granules and small acid phosphatase-positive particles with myelin body formation, is a probable manifestation of lysosomal aging. The lipid content noted during this phase may be owing to a lack of lipolytic enzymes in the hydrolytic enzyme complement.

Pathologic Implications of the Lysosome Hypothesis

The interrelations of the morphologic states postulated in the lysosome hypothesis (Chart 2) provide a framework for examining lysosomal function and dysfunction. Table 3 outlines a basic schema for the classification of lysosomal involvement in pathologic states.

Defects in lysosomal enzyme synthesis and/or abnormalities in the process of vesiculation are noted. Of interest in this respect are the observations of Austin and coworkers,[2] who demonstrated a specific lack of lysosomal arylsulfatase A and B in the genetically determined neurologic demyelinating condition, metachromatic leucodystrophy, in which there is an accumulation of neuronal sulphatide. Hers[35] demonstrated a lack of α-glucosidase in glycogen storage disease Type II (Pompe). In this disorder, there is abnormal storage of glycogen, but electron micrographs have demonstrated that the glycogen is intravacuolar as opposed to storage of free cytoplasmic and nuclear glycogen seen in the other kinds of glycogenosis. Of related interest is the genetic disparity in the presence of β-glucuronidase in the liver of various mouse strains.[58] Conversely, Austin and coworkers[2] demonstrated an increased amount of intralysosomal arylsulphatase B in gargoylism, a condition manifested by increased urinary excretion of sulphated mucopolysaccharide-like materials. Knowledge concerning probable defects in the process of vesiculation is scant, but an abnormality in the Golgi vesicular and saccular profiles has been noted in neurons in Vitamin E deficiency[49] and also in the early phases of starvation. Storage granule formation is a manifestation of part of the lysosomal mechanism. A defect in the normal extrusion of such a stored, functionally prepared particle is seen in the inhibition of zymogen degranulation following the feeding of β-3-thienylalanine.[40] The genetically induced condition of constitutional hyperbilirubinemia is accompanied by peribiliary dense body accumulation.[34] Irradiation to the thyroid gland (I^{131}) inhibits normal thyroid stimulating hormone (TSH) stimulation and extrusion of thyroid hormone into the circulation following fusion of the pinocytosed thyroglobulin with dense bodies.[64]

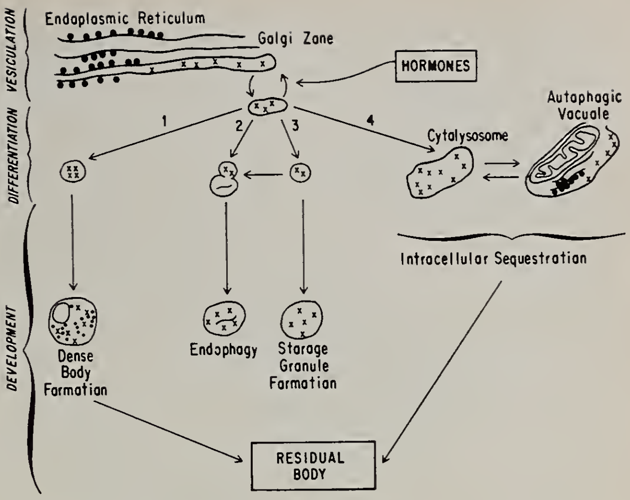

Chart 2.—Diagrammatic representation of the genesis, evolution and morphologic forms encompassed by the lysosome concept.

Intracellular "indigestion" has been suggested to occur in states of abnormal intracellular storage

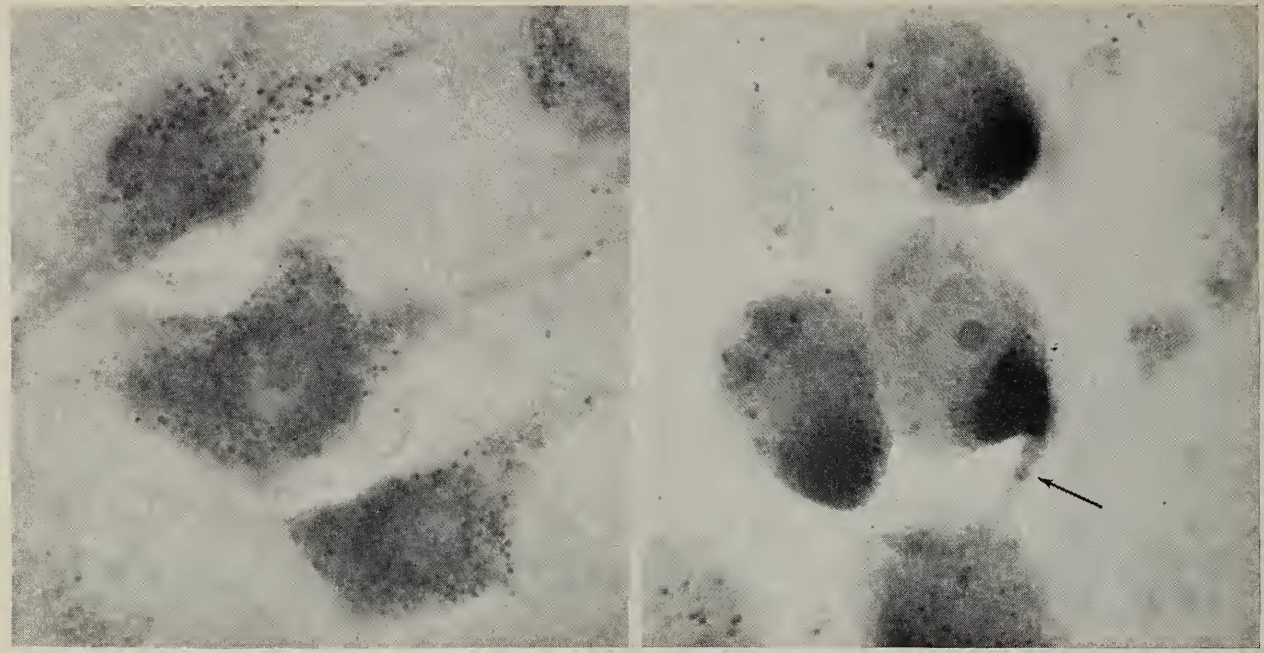

Figure 2.—Showing polar migration of lysosomes to axon hillock with cytolysosome formation, six days following subacute administration of IDPN (β,β-iminodioproprionitrile). Arrow indicates proximal segment of axon. The nucleolus is easily identified both in control animals and those injected with IDPN. The lysosomes are regularly dispersed through the perikaryon and apical dendrites in the control animal. Nuclei of reticular formation of adult mouse, Gomori acid phosphatase procedure following perfusion fixation (×100).

in which there is increased lysosomal activity. Diseases such as hemosiderosis, hepatolenticular degeneration[31] and osmotic, bile and hemoglobinuric nephrosis, are considered natural examples of these abnormal storage phenomena. Moreover, glycogenosis Type II is characterized by an abnormal storage of glycogen. Experimentally induced abnormal storage of high molecular weight substances; for example, Triton WR-1339[90] has also been seen. Chart 2 indicates that cytolysosome and autophagic vacuole formation as a form of intracellular sequestration occurs. This phenomenon has been noted in accentuated form following neuronal irradiation, starvation and Vitamin E deficiency, and also in pancreatic acinar cells following the administration of various substances which inhibit protein synthesis. In the later stages of amphotericin B induced renal disease, Scarpelli and coworkers [71] demonstrated mitochondrial swelling, increased numbers of lysosomes and cytolysosomes containing double membrane fragments and calcific deposits. Lysosomes have been identified in light and electron microscopic examination of Gomori-treated tissue from the renal papillae of rats fed a potassium deficient diet.[57] Noteworthy is the naturally induced prostatic epithelial involution following estrogen therapy and castration in which extensive cytolysosome formation is evident.

A more subtle manifestation of lysosomal disorder has been demonstrated following β, β-iminodiproprionitrile administration to mice, which promotes a state of hyperexcitability and bizarre circling.[85] Histochemically there is widening of the Golgi lamellae with fragmentation and enlargement of lysosomes with migration to the axon hillock (Figure 2). A similar dendritic and axonal localization of lysosomes is seen during the neonatal period. Thyrotropic stimulating hormone (TSH) promotes a trans-cellular migration of lysosomal particles from the storage (colloid) epithelial boundary to the perivascular epithelial membrane[64].

An increase in residual body formation has been noted following triparanol and in Tay-Sachs disease in which an excessive number of bizarre myelin figures and membranous cytoplasmic inclusions are noted. In premature aging, there is an accentuation of neuronal, hepatic, smooth muscle and cardiac lipofuscin granules, thought to represent lysosomal residual bodies.

Probably of greatest interest from the pathologic point of view, although somewhat speculative, are those situations in which a "labilization" or activation of the lysosomal particles with release of enzymes, is noted (Table 3). Fell and Mellanby in 1952 observed a progressive loss of metachromatic material and glycogen from the matrix of embryonic cartilage when grown in a medium containing excess vitamin A.[26] Subsequently, the hypothesis was developed that vitamin A acted upon the lysosomal membrane with release of acid proteases,[27,29] which in turn were capable of degrading the cartilage matrix.[20] An extensive chondromalacia in adult cartilage is also seen in hypervitaminosis A. It is tempting to suggest that the chondromalacia and loss of metachromasia seen in the trachea, costal, auricular and nasal cartilages in relapsing polychondritis may in fact be due to lysosomal activation in the chondrocyte.[82] The possibility exists that this may represent an autoimmune response, as lysosomal activation has been reported following incubation of lysosomes with heterologous antibody,[91] streptolysin O[95] and within ascites tumor cells by specific antibody.[8] Cellular hypoxia is a potent stimulus to hepatic lysosomal activation[21] and evolution[16] although the exact mechanism is unknown.

While the foregoing considerations of lysosomal activation suggest that focal cellular degradation may occur following the leakage of these hydrolytic enzymes into the neighboring cytoplasm, a stabilization of the lysosomal membrane has been demonstrated in the presence of hydrocortisone,[96] cholesterol,[24] chloroquin[92] and some antihistamines.[45,81] *In vivo,* cortisone has been shown to protect against the cartilage lesions of hypervitaminosis A,[28,94] shock, endotoxemia[93] and fibroblast cytotoxicity induced by antilysosomal antibody.[91]

Conclusion

The comments raised in this review are based upon morphologic and biochemical observations of a cell fraction rich in acid hydrolases. The interrelations of pinocytic and phagocytic vacuoles with storage granules, digestive vacuoles and dense bodies is summarized. Strikingly, we have little evidence of the origin of the hydrolases in the dense bodies, although examples of hormonal control of this process are suspected. The role of the lysosome in phagocytosis and intracellular digestion is a natural extension of the "cytase" hypothesis of Metchnikoff[55] proposed to elucidate the role played by macrophages and leukocytes in the defense of the organism against bacterial invasion.

In conclusion, a word of warning. The protean manifestations of the modern role for the lysosome are far removed from de Duve's original concept. It is to be admitted that some pathologic phenomena mentioned herein bear a very tenuous relation

TABLE 3.—*Disordered Lysosomal Function in Pathologic Conditions*

A. GENETIC AND ACQUIRED DEFECTS IN LYSOSOMAL ENZYME SYNTHESIS:
   1. Metachromatic leucodystrophy — absence in arylsulphatase A & B.[2]
   2. Glycogen storage disease, Type II—absence of α-1,4-glucosidase.[35]
   3. Genetically induced β-glucuronidase deficiency in mice (C3A/Ha).
   4. Gargoylism — increased lysosomal arylsulphatase B[2]

B. DEFECT IN GOLGI VESICLE AND VACUOLE FORMATION:
   1. Starvation.[65]
   2. Vesicular proliferation in Vitamin E deficiency.[49]

C. DEFECT IN LYSOSOMAL EXTRUSION:
   1. I^{131} irradiation to thyroid.[64]
   2. Inhibition of zymogen granule secretion following β-3-thienylalamine administration.[40]
   3. Constitutional hyperbilirubinemia (Dubin-Johnson syndrome).[34]
   4. Botulinum toxin induced block of neurohumoral transmitter release.[78]

D. ABNORMAL INTRALYSOSOMAL STORAGE:
   1. Glycogen storage disease, Type II.[35]
   2. Osmotic,[53] hemoglobinuric[56] and bilirubin nephrosis.[61]
   3. Siderosis,[17,30] Wilson's hepatolenticular degeneration.[31]
   4. Ingestion of high molecular weight substances, e.g. polyvinylpyrolidone[54] clinical dextran,[51] Triton WR-1339.[90]

E. INCREASED CYTOLYSOSOME AND/OR AUTOPHAGIC VACUOLE FORMATION:
   1. Vitamin E. deficiency.[49]
   2. Acute starvation.[65]
   3. Following administration of glucagon[1]; β-3-thienylalanine, azaserine and triparanol[41,42]; amphotericin B induced nephropathy.[71]
   4. Hypokalemia.[57]
   5. Hypoxic liver injury.[16]
   6. Axon section[3,43,63]; neuronal irradiation.
   7. Phytohemagglutination stimulation in lymphocytes.[37]
   8. Involutional changes in prostatic epithelia induced by castration and estrogens.[9]

F. DISTURBANCE IN INTRACELLULAR LYSOSOMAL MOVEMENT:
   1. Biliary obstruction.[65]
   2. β,β-iminodiproprionitrile (IDPN) induced neuroazonal dystrophy.[85]
   3. TSH induced thyroid follicle stimulation.[64]
   4. Neonatal neuronal distribution.[6,80]

G. INCREASED RESIDUAL BODY FORMATION:
   1. Aging (natural and irradiation induced).
   2. Triparanol administration.[76]
   3. Tay-Sachs disease.[88]

H. INTRACELLULAR "LABILIZATION" OF LYSOSOMAL ENZYMES:
   1. Lipid peroxidation[77] (Vitamin E deficiency, ionizing irradiation).
   2. Vitamin A.[20,27,29]
   3. Streptolysin O and S,[95] endotoxin,[44,93] heterologous antibody.[91]
   4. Hypoxia.[21]
   5. Carbon tetrachloride hepatotoxicity.[19]

to the biochemical concept. In contradistinction, however, is the wealth of provocative information and speculation which the concept has engendered and which in modified form may be shown to be related to the phenomena of acetylcholine and catecholamine release at the presynaptic plate following membrane fusion of the synaptic vesicle or degranulation in mast cells with release of histamine upon exposure of sensitized cells to antigen.

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CASE REPORTS

Acute Herpes Zoster

Successful Treatment by Continuous Epidural Analgesia

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HERPES ZOSTER is an acute disease affecting primarily the posterior root ganglia of the spinal nerves. The thoracic nerves are most frequently involved and the disease is usually unilateral. The pain, which has a dermatomic distribution, progresses in severity and is stabbing in character. It is accompanied by crops of vesicular lesions which are characteristic of the disease. The severity of pain in acute herpes zoster is almost directly proportional with advancing age, and in the age group of 70 years or older, severe pain persists in almost 50 per cent of patients for more than a year.[3]

Although the word *herpes* has been used in medicine for a least 25 centuries, no specific therapy for herpes zoster exists.[1] Many therapeutic measures have been tried, including the use of intravenous sodium iodide, sodium salicylate, cobra venom, massive doses of vitamin B, antibiotics, corticosteroids, ethyl chloride spray, diathermy and deep radiotherapy.[6]

The use of nerve blocks in the treatment of herpes zoster was first reported by Rosenak in 1938.[7] Since that time there have been reports of a fair degree of success obtained by the use of paravertebral nerve blocks or the intravenous administration of procaine or a combination of these measures.[8] In a search of the literature no reports were found of the use of continuous epidural analgesia in the therapy of acute herpes zoster.

In order to provide complete relief from pain without the disadvantages of central nervous system depression, the most feasible therapeutic modality is that which produces interruption of the pain pathways peripherally. Extradural blockade of the appropriate dermatomic segments relieves both somatic and visceral pain and abolishes reflex muscular spasm.[9] This method of treatment permits the patient to remain alert, cooperative and free from respiratory depression. Segmental epidural analgesia has been suggested as being superior to any other method of managing postoperative pain.[2]

Herein is reported the successful use of continuous epidural analgesia in the treatment of severe herpes zoster in a critically ill, aged patient.

Report of a Case

A 70-year-old Caucasian man was admitted to the hospital with acute severe pain of one week's duration, involving the lower right rib cage. This was accompanied by a rash with blebs and erythema covering the full extent of the dermatomes of the sixth, seventh, eighth and ninth thoracic nerves on the right side of the chest wall. The patient complained of continuous burning discomfort associated with lancinating pain. Hyperalgesia and hyperaesthesia were also present. The patient said that the pain was excruciating. He required 600 mg a day of meperidine for minimum relief.

The history of the patient included several epi-

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sodes of severe myocardial infarction, several cerebral vascular accidents and chronic uremia. Because of an atonic bladder, the patient had an indwelling suprapubic catheter. Electrocardiographic tracings were consistent with old infarction of the anterior myocardial wall and the inferior myocardium. The patient was receiving anticoagulant therapy.

The complexities of the total physical situation and the intractable nature of the pain necessitated therapeutic improvisation. Continuous epidural analgesia was selected.

Because the herpetic lesions extended over the area for mid-thoracic block, the plan decided upon was to insert a plastic catheter at a lower level and thread it cephalad. This would allow the patient freedom of movement. Analgesia would be obtained by bathing the epidural space with a local anesthetic solution, administered by continuous drip. In elderly arteriosclerotic patients the spread of analgesia is significantly greater than in other patients of similar age.

First day. Under sterile precautions, a 17-gauge Touhy needle was inserted in the interspace between the first and second lumbar vertebrae. When the epidural space was entered, a vinyl plastic catheter was placed and threaded slowly upward to approximately the eighth thoracic segment and 10 ml of lidocaine 1.5 per cent was injected. Complete relief from pain was obtained within ten minutes. The needle was removed and the epidural catheter left in situ, the exposed end being taped to the patient's back. A continuous drip of 0.4 per cent solution of lidocaine with epinephrine 1:200,000 dilution in 1,000 ml of 0.45 per cent saline solution was set up for constant flow. The patient was very comfortable and moved his extremities well. An hour after the first injection, the blood pressure suddenly fell from 100/80 mm of mercury to 70/50 and the patient began to sweat profusely. Oxygen was administered by mask and an intravenous drip of 5 per cent dextrose in water was instituted. Methoxamine 4 mg was administered slowly and the blood pressure was brought up to 100/70 mm of mercury within 30 seconds. The patient's condition improved. An electrocardiogram taken at that time showed changes consistent with a new anterior myocardial infarction. An hour later, his condition stabilized, the systolic blood pressure varying from 90 to 100 mm and the pulse rate regular at 88. The skin was again warm and dry and the patient moved his extremities without impairment. The epidural catheter drip was begun at a rate permitting 50 mg of lidocaine per hour. Four hours later the blood pressure had risen to 120/80 mm of mercury and the patient was comfortable and cheerful. He spent a comfortable night.

Second day. Pain in the herpetic area was completely relieved, but the patient complained of substernal precordial pain. An electrocardiogram showed changes from that of the preceding day indicating progression of the new infarction. For the next 24 hours 0.4 per cent lidocaine without epinephrine was used for the drip infusion.

Third, fourth and fifth days. The patient required 60 mg lidocaine per hour for complete comfort.

Sixth and seventh days. The concentration of lidocaine had to be increased to give 75 mg an hour during waking hours but 50 mg an hour was sufficient during sleep.

Eighth day. The patient was still completely comfortable.

Ninth day. The blood pressure fell to 80 mm of mercury systolic and the patient again complained of precordial pain. There was no loss of consciousness at any time. An electrocardiogram showed no further progression of the previously noted infarction. Oxygen was again administered by mask and the blood pressure rose to 140/70 mm of mercury. The patient said he was very comfortable and felt fine.

Tenth day. No complaints except of intermittent substernal discomfort occasionally.

Eleventh day. The patient complained of pain in the posterior aspect of the left thigh. It was thought that this might be due to the pressure of the epidural catheter. After eleven days of continuous lidocaine drip, the epidural catheter was removed. Smears from the puncture site, as well as the intra-epidural portion of the catheter were sent to the bacteriological laboratory for study. All cultures were reported sterile. By this time the herpetic lesions were drying up and the patient was comfortable. The pain in the thigh subsided within three days.

Discussion

Continuous epidural analgesia was attempted in the treatment of acute herpes zoster. The therapeutic effect of the block on the herpetic pain was most remarkable. The catheter was left in the epidural space for 11 days, which is the longest recorded period for this technique. The reported principal hazards of continuous epidural catheter techniques have been epidural infection[4] and catheter breakage.[5] Neither occurred in this case.

Summary

A case of acute herpes zoster was successfully treated by continuous epidural analgesia. The catheter was left in place for 11 days without infection.

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Occult Neoplasm Causing Syndrome of Retroperitoneal Fibrosis

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RETROPERITONEAL FIBROSIS is one name for a syndrome which includes the gradual obstruction of one or both ureters by a hard fibrous plaque which is often, although not always, limited to the periureteral regions. The process has also been called *periureteritis plastica, periureteritis obliterans, perirenal fascitis, periureteral lymphangitis, periureteral liposclerosis, Gerota's fascitis, retroperitoneal adiponecrosis, idiopathic non-specific fibrosing retroperitonitis* and *Ormond's syndrome.* As is usually the case when a disease is endowed with a myriad of descriptive tags, the pathologic history is obscure. Many efforts have been made to find a cause for this disease, but the more than 125 cases thus far reported resist classification by pathogenesis.

Certain neoplastic diseases which are sometimes associated with pronounced fibrotic reaction have been suggested as causative factors. These include Hodgkin's disease and other lymphomas, certain sarcomas and anaplastic carcinomas that spread to the retroperitoneal space. Post traumatic or post surgical scarring has been impugned as an etiologic possibility. When the retroperitoneal inflammation includes fatty tissue and takes a form of a granulomatous reaction, the process has been called *sclerosing lipogranuloma.* Retroperitoneal fibrosis has been considered as part of a generalized hypersensitivity phenomenon as seen in periarteritis nodosa or Wegener's arteritis. Severe urinary tract infection of long standing has been suggested as a cause, as have actinomycosis and other fungus infections. In some cases there has been an associated inflammatory condition of the bowel, pelvis or lower extremity. Some patients have had aortitis. In others, lymphangitis (or at least involvement of the lymphatics with edema of the lower extremity) has been a prominent feature. Experimentally, the presence of urine in the retroperitoneal space has been shown to cause fibrotic reaction. Syphilis classically produces fibrotic tissue but in only one of the cases reviewed was positive reaction to a serologic test for syphilis reported. Recent reports indicate that the anti-

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serotonin agent methysergide maleate (Sansert®), is the one known etiologic agent.

Unfortunately, pathologic examination of the fibrous plaque has not been too helpful. The cellular component is variable and often scant. Generalized vasculitis is usually seen but it is non-specific. The prominent feature is firm uniform fibroblastic proliferation which is found behind the peritoneum on either or both sides as far lateral as the lumbar gutters. It has been found as low as the level of the trigone and as high as the diaphragmatic crura.

Reports of Cases

CASE 1. A 29-year-old white machinist was first seen on December 12, 1963 with acute left ureteral colic. Except for a low backache of two weeks' duration he said he had no pains. His general health had been excellent. He had not had fever, chills, nausea or frequency of urination. No masses were palpable in the abdomen and there was no tenderness in either costovertebral angle or in the abdomen. No muscle guarding was evident but a left psoas sign was equivocally positive. No lymph nodes were palpable and no hernia was present. External genitalia were normal. The rectal sphincter was thickened as the result of a previous operation for a perirectal abscess. The prostate gland was normal in size and texture and no abnormal rectal masses were felt. Results of urinalysis were within normal limits. An excretory urogram showed promptly functioning kidneys of equal size and without dilatation. In retrospect the ureters were slightly deviated medially on these films. Tentative diagnosis was made of a passed left ureteral calculus.

Eight weeks later the patient was seen again, complaining of progressively severe pain in the left lower abdominal quadrant, radiating down the backs of both thighs. He required increasing amounts of morphine. He was weak and pale without signs of overt bleeding. He said he had had no difficulty in evacuation of bowel or bladder. Physical examination was unchanged except for pallor and mild spasm of the paravertebral muscles. Results of urinalysis again were within normal limits. No abnormalities were seen in roentgenograms of his chest. Hemoglobin, which had been 14.5 gm per 100 ml at the time of the previous examination, now was 9.0 gm. Erythrocyte sedimentation rate was 115 mm in one hour (Wintrobe). An excretory urogram demonstrated no function on the right in two hours and minimal left caliectasis without pyelectasis. The bladder outline appeared normal and the bladder emptied well, judging from the post voiding film.

Cystoscopic examination and retrograde pyelograms were carried out on February 11, 1964. The bladder and urethra were normal. A ureteral catheter passed easily to the left kidney and pyelograms confirmed the presence of mild caliectasis. The right ureteral catheter met mild resistance approximately 6 cm from the bladder, but then passed easily to the kidney, which was evacuated of 45 ml of clear urine. Right retrograde pyelograms revealed moderate hydronephrosis. The right ureteral catheter was left in place and splinted with an indwelling urethral catheter. In the differential diagnosis retroperitoneal fibrosis and a retroperitoneal malignant lesion involving both ureters were considered.

Transperitoneal exploration was performed February 13, 1964 through a midline incision. A large plaque of hard smooth fibrous material encased the ureter on the right and extended from below the sacral promontory to the renal arteries. To the left of the midline a narrow tongue of fibrous tissue extended across the aorta, partially encasing the left ureter. The right ureter was freed from the mass with difficulty while the left was easily freed from its relatively superficial involvement. Both ureters were transplanted intraperitoneally. A generous biopsy specimen was taken from the mass near the level of the fifth lumbar vertebra on the right, permitting some necrotic material to ooze from the center of the plaque. Microscopic examination revealed "non-specific inflammation with fibrosis." The slides were examined by two oncologists who agreed regarding the benignity of the lesion. Routine cultures from the caseous material produced no growth.

The patient's immediate postoperative course was ordinary. He regained strength and pain was not prominent. He was given a total dose of 900r of x-irradiation to both lumbar gutters from midsacrum to diaphragm.

A month later he began to have severe pain in both flanks which radiated anteriorly around the pelvic girdle and into the subcostal regions. Roentgenograms of the chest showed decided widening of the upper mediastinum. X-irradiation was resumed and extended to include the mediastinum. In addition the patient was given dexamethasone 0.5 mg 3 times daily. Dramatic relief followed and the patient returned to work in 48 hours. However, debilitating flank and pelvic pain soon recurred.

The patient was readmitted to the hospital where roentgenograms of the chest showed decided extension of the mediastinal mass into the upper lung fields. Biopsy of enlarged lymph nodes felt in the left supracervical region showed reticulum cell sarcoma. The patient died June 24, 1964 with widely disseminated tumor.

CASE 2. A 57-year-old woman of Mexican extraction was examined by an internist in September 1962 for weakness and anemia of unknown cause. She complained that eating large meals produced excessive epigastric fullness. She had had no loss of weight, no urinary difficulty, no abdominal pain and no hematuria. Previous operations included a hysterectomy for benign fibromyomata 10 years previously and appendectomy five years before that. On physical examination the only abnormality noted was a smooth, fixed, non-tender mass approximately 6 cm × 12 cm deep in the left mid-abdomen. It was not palpable through the vagina or rectum. Hemoglobin was 11.9 gm per 100 ml of blood. Leukocytes numbered 10,250 per cu mm and the cell differential was within normal limits. Erythrocyte sedimentation rate was 29 mm in one hour (Wintrobe). An excretory urogram revealed non-function of the left kidney. No abnormalities were seen in roentgenograms of the intestinal tract and chest. Cystoscopic examination and left retrograde pyelograms were carried out September 19, 1962. The bladder and urethra appeared normal. A ureteral catheter was passed to the left kidney with ease but a left ureterogram revealed pronounced narrowing of the left mid-ureter for approximately 8 cm. Urine specimens from the left kidney and bladder were negative for malignant cells. No growth resulted from routine cultures. The left kidney showed slight atrophy and no hydronephrosis. The presumptive diagnosis was retroperitoneal fibrosis limited to the left side.

On September 24, 1962 a left lumbar incision was made and a thick, white, fibrous mass was seen forming a sheath about the left ureter from the renal pedicle to the level of the bifurcation of the common iliac artery. The kidney appeared normal. The peritoneum was easily separated from the mass and the left ureter was transposed to an extraperitoneal position. Biopsy of the fibrous mass revealed "non-specific inflammation with fibrosis." Postoperative recovery was normal, but gradually pain developed in the left flank. Six weeks after operation an excretory urogram showed no return of left renal function in four hours. On retrograde studies the left ureter was seen to be patient. Radioactive renograms demonstrated no function on that side. Because of progressive left abdominal pain, x-irradiation amounting to 1150 r in air was given during a two-week period. The left abdominal mass diminished and became non-palpable. Pain persisted and the left kidney did not return to function. On April 1, 1963 left nephrectomy was carried out. At operation the fibrotic process was seen to involve the renal pedicle but it showed no sign of extending across the midline. No abnormalities were noted on peritoneal exploration. The removed kidney showed chronic non-specific phelonephritis with atrophy. The patient recovered and pain was relieved.

On the 14th postoperative day, the surgeon noted a 2×3 cm mass on the left side of the patient's neck. It was soft and movable and felt like an enlarged lymph node. She was examined by a general surgeon and excisional biopsy was scheduled two weeks later but by that time the mass had disappeared and the biopsy was canceled.

Approximately a year and a half after ureterolysis and a year after nephrectomy the patient brought to our attention a small hernia through the lumbar scar. An excretory urogram showed a hypertrophied but otherwise normal right kidney. The patient had no pain but wished to have the hernia repaired.

As it happened, it was at this time that the young machinist in Case 1 was found to have malignant disease and we recalled the peculiarly transient node in this woman's neck. On careful reexamination no lymph nodes were felt in her neck or elsewhere. Nonetheless, at the time of lumbar herniorrhaphy on April 16, 1964 nodes were removed from the left scalene fat pad and on biopsy giant cell lymphosarcoma was diagnosed.

Discussion

The delayed finding of malignant disease in these two cases led us to explore the literature and carry out personal communication in an attempt to ascertain the frequency of this situation. We were impressed by the lack of documented follow-up in cases of so-called "benign idiopathic retroperitoneal fibrosis." We would like to know if five-year follow-up will alter the 7 to 16 per cent mortality rates now reported in the literature.

As discussed above, the cause and exact nature of this disease are poorly understood and highly speculative. It is commonly considered a benign entity and discussed as such.

In the two patients reported upon herein, careful gross and microscopic examinations were made, the disease was deemed benign and, therefore, presumably the patients were cured or at least assured of a reasonable prognosis by adequate surgical treatment. One is dead from a reticulum cell sarcoma which in retrospect was in part (or entirely) the original process. The other patient is now known to have a sarcoma but ultimate evaluation of its relationship to the original retroperitoneal findings must await autopsy.

The fortuitous finding a lymphoma in the second case by scalene biopsy prompts us to recommend that such biopsy be a part of the evaluation of all patients with suspected retroperitoneal fibrosis.

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An Unusual "Thyroid" Nodule "Cold" to Scintiscan

KENNETH R. MC CORMACK, M.D.
San Francisco

RADIOISOTOPE SCINTISCANNING is widely employed in the clinical evaluation of thyroid nodules. When a nonfunctioning ("cold") solitary nodule is demonstrated, potential thyroid malignant disease is suspected. The incidence of confirmed carcinoma in such cold nodules varies and has been reported to be as high as 55 per cent.[2]

Various benign lesions will result in the appearance of a cold nodule on scintiscanning. These include cystic changes, degeneration, necrosis, hemorrhage and nonfunctioning adenomas. In the following case report, another type of benign lesion is described, which produced a solitary cold area on thyroid scintiscan.

Report of a Case

A 58-year-old Caucasian woman was admitted to the University of California San Francisco Medical Center on August 2, 1964. Except for intermittent joint discomfort attributed to arthritis, she had been in apparent good health until June 1964. At that time she had noted sudden onset of severe pain in the region of the right groin. Two weeks later roentgenograms of the right femur revealed an osteolytic lesion in the neck and another in the shaft. A metastatic carcinoma was suspected and the patient was admitted to another hospital for further study on July 13, 1964.

On the initial admission, mild hypertension was noted (blood pressure 170/90 mm of mercury). The thyroid gland was diffusely enlarged. The right lobe was larger than the left and it contained a 2 x 2 cm mass in the midportion. Moderate kyphoscoliosis was observed and pain was elicited on movement of right hip. The serum calcium level was

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From the Nuclear Medicine Section, Department of Radiology, University of California School of Medicine, San Francisco.

Submitted February 25, 1965.

reported as 15.3 mg per 100 ml and serum phosphorus 3.3 mg per 100 ml. A biopsy of one of the lesions in the proximal right femur resulted in a histologic diagnosis of osteitis fibrosa cystica ("brown tumor" of hyperparathyroidism).

On admission of the patient to the University of California San Francisco Medical Center, roentgen studies were repeated. The well defined lytic lesions involving the proximal right femur were again noted (Figure 1). Generalized bony demineralization was also present and an anterosuperior mediastinal soft-tissue mass was suggestive of substernal extension of the palpable goiter (Figure 2).

Thyroid uptake of radioiodine was 22 per cent in 24 hours. The scintiscan showed an enlarged gland with function extending down to the sternal notch when the patient's neck was extended. In the midportion of the right lobe, function was diminished in an area of 3×4 cm (Figure 3). Arteriographic studies of the aortic arch on August 7, 1964 showed enlargement of the right inferior thyroidal artery. The branches led to and surrounded the nodule in the midportion of the right lobe, but without demonstrable "tumor blush" (Figure 4).

Operation was carried out August 13, 1964. The mass, which was 4×5×3.5 cm and weighed 34 grams, occupied the midportion of the right lobe. It was a parathyroid adenoma. Smaller parathyroid adenomas were located at each inferior pole of the thyroid gland. The entire right lobe and the upper and lower poles of the left lobe were removed. The posterior view of the excised specimen, with the largest adenoma transected for better exposure, is shown in Figure 5. The histologic pattern of the tissue within the largest nodule is shown in Figure 6. No abnormal thyroid tissue was seen in multiple sections of the excised gland.

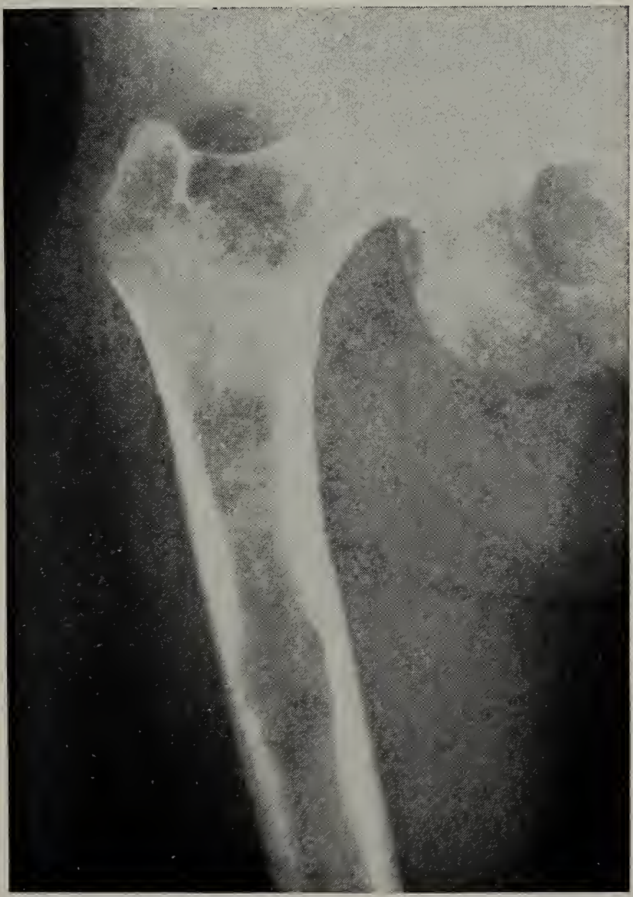

Figure 1. Anteroposterior view of the proximal right femur showing a lytic defect in the neck and a second lesion in the midshaft. The margins are smoothly outlined and no cortical reactive new bone is identified.

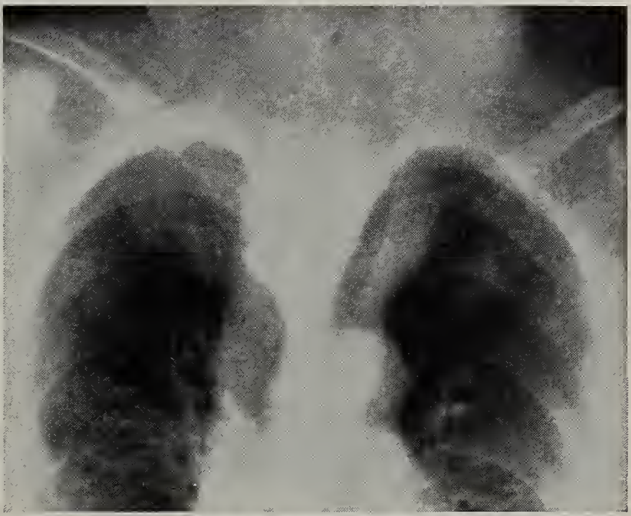

Figure 2. The soft-tissue mass is seen in the upper right mediastinal area, with displacement of the air-filled trachea to the left.

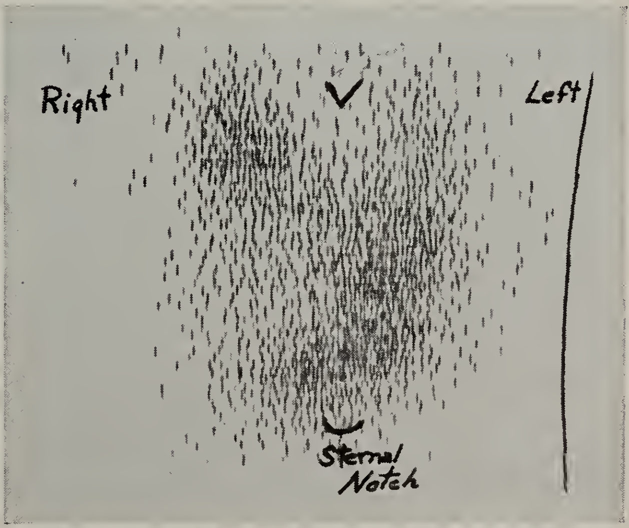

Figure 3. Scintiscan of the thyroid gland showing a 3×4 cm area of diminished concentration of radioactivity over the palpable, localized enlargement on the right side. Tissue that concentrates radioiodine extends to the level of the sternal notch when the neck is extended for the scintiscan.

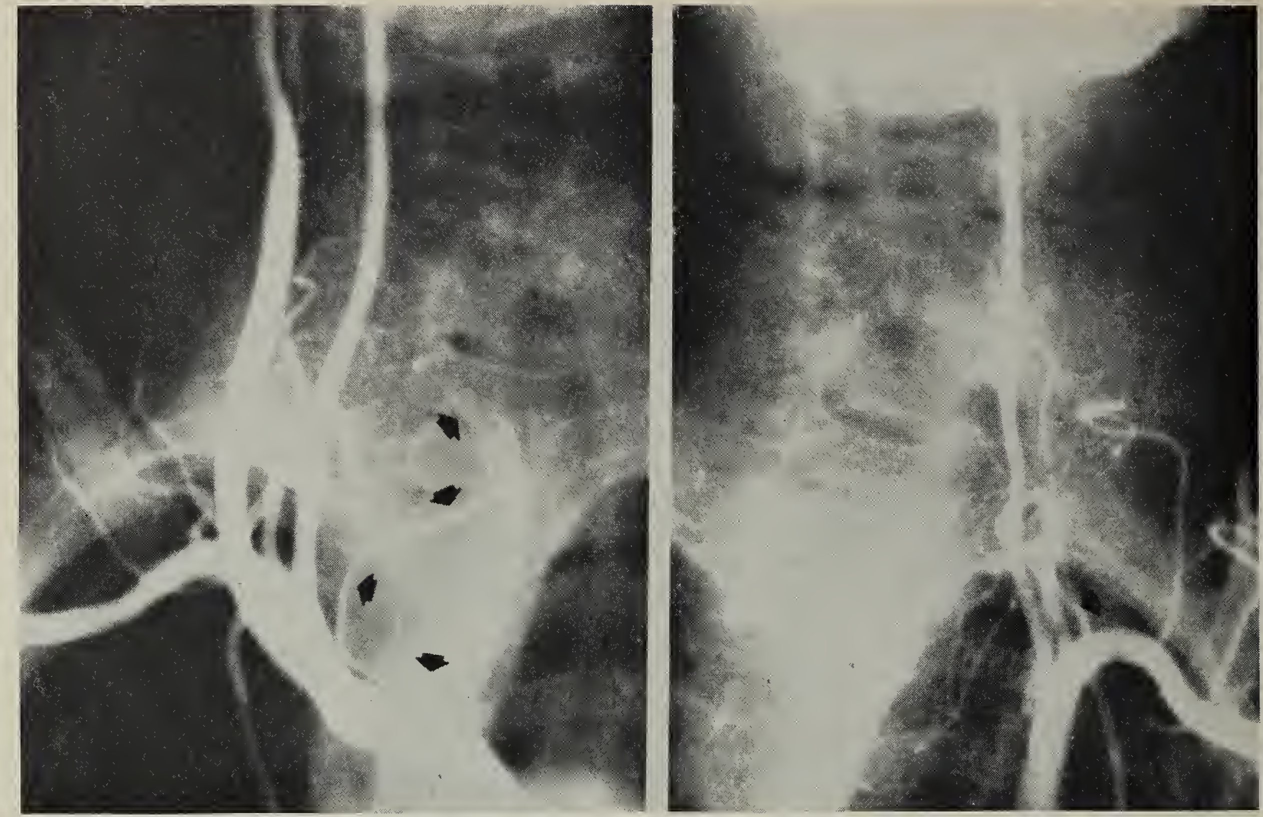

Figure 4. Arteriographic studies of branches of the aortic arch. Film at left shows enlargement of the inferior thyroid artery on the right side. Peripheral branches (arrows) surround the parathyroid adenoma but no "tumor blush" was seen. For comparison, the film at the right shows the normal sized inferior thyroid artery on the left (arrow near its origin).

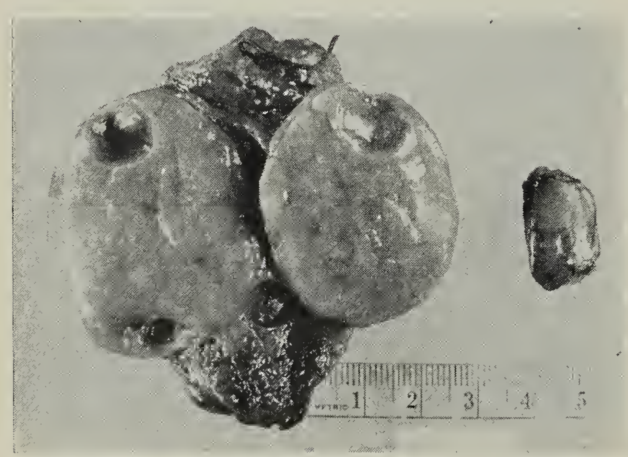

Figure 5. Posterior view of the excised surgical specimen. The parathyroid adenoma has been transected for exposure. One of the smaller adenomas is shown on the right.

Chemical elements in the blood quickly reverted to normal levels after the operation and the patient was discharged from the hospital August 29, 1964.

Discussion

Any lesion represented on the scintiscan as a cold nodule within the functioning area of a thyroid gland is usually considered as thyroidal in origin. The appearance of a cold nodule on the scan increases the probability of carcinoma, but it may also be the result of a variety of benign lesions.

In the present case hyperparathyroidism had been established before the surgical procedure. The diagnosis was based on the lytic lesions in the right femur and the characteristic changes in chemical factors in the blood. A coexistent thyroid carcinoma, nevertheless, had still been considered a possibility. The size, the substernal extension and the scintiscan pattern of the soft tissue mass supported a probability of thyroid rather than parathyroid origin. The incidental finding of thyroid carcinoma in eight previous patients explored surgically for parathyroid adenomas[1] lent credence to the possibility of thyroid carcinoma. The enlarged inferior thyroid artery on the right side, seen angiographically, was similar to such consistent enlargement on the side of the parathyroid adenoma as recently described by State.[3] No vascular blush had been noted to support the possible diagnosis of thyroid carcinoma. Biopsy of the frozen section and the final histologic sections confirmed that this mass was a large parathyroid adenoma. A parathyroid

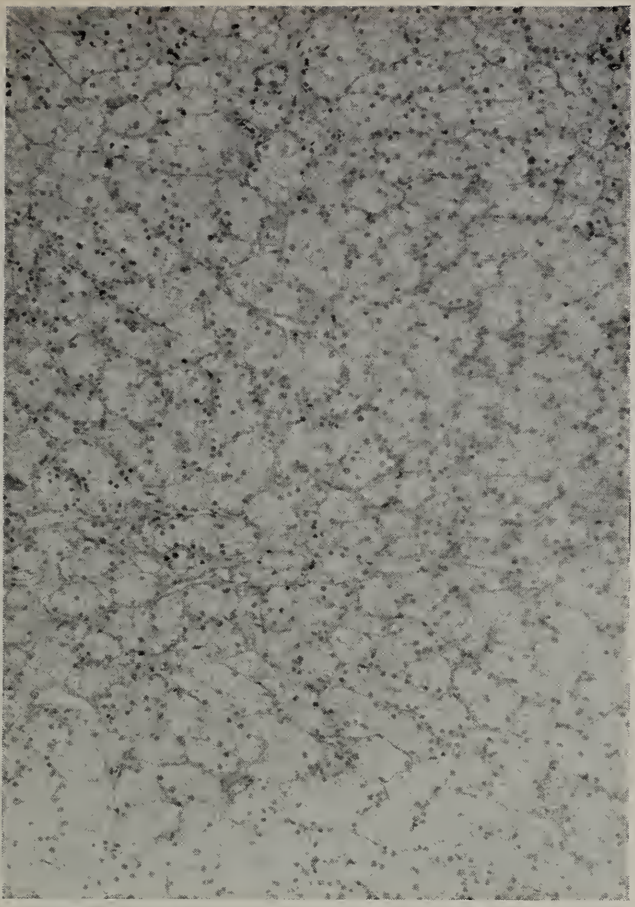

Figure 6. Histologic section of the tissue in the large parathyroid adenoma (×100). All sections of the large and smaller adenomas showed a similar uniform pattern of primary hyperplasia.

scintiscan with 75-Se selenomethionine was not obtained in this instance. It might have proved the most helpful preoperative diagnostic test in identifying this large cold nodule in the thyroid gland.

Summary

A lesion of unusual type produced a "cold" area within the thyroid gland on a scintiscan study. This lesion proved to be a large parathyroid adenoma rather than the suspected thyroid carcinoma coincident with hyperparathyroidism.

Department of Radiology, University of California Medical Center, San Francisco, California 94122.

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An Unusual Roentgen Sign in—

Gangrenous Appendicitis

ROBERT W. PETERSEN, M.D.
Santa Monica

A CAREFUL CLINICAL EVALUATION of the patient is usually decisive in the diagnosis of acute appendicitis. Rarely is it necessary to depend upon a roentgen study of the abdomen, although in some instances such an examination can be helpful. For example, in acute appendicitis with calculi (enteroliths), or acute appendicitis with abscess formation, the radiological study is frequently confirmatory. A reflex ileus is quite usual with acute appendicitis, as in other intra-abdominal inflammatory conditions. When peritoneal reaction has occurred, there may be blurring of the pro-peritoneal fat line.

Rarely is gas visualized within the appendix. As Samuel[4] pointed out, with anatomical variations in the position of the cecum, the appendix may represent the highest point of the right half of the colon, and in this location may contain intestinal gas. Hence, even if gas is seen within the appendix, the pathological significance of the phenomenon should be viewed with skepticism if the organ is in the right upper quadrant.

Frimann-Dahl[2] mentioned that sometimes gas in an inflamed appendix or an abscess is mixed with thick pus and has a "foam-like" appearance on an x-ray film. However, he did not stress that gas within the appendix is a sign of appendiceal disease.

Fisher[1] reported a case of gangrenous appendicitis in which roentgenographic demonstration of a dilated fixed appendix containing gas and a fluid level led to the correct diagnosis before operation. This was the first documented case of appendicitis

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From the Department of Diagnostic Roentgenology, Cottage Hospital, Santa Barbara.

Submitted February 15, 1965.

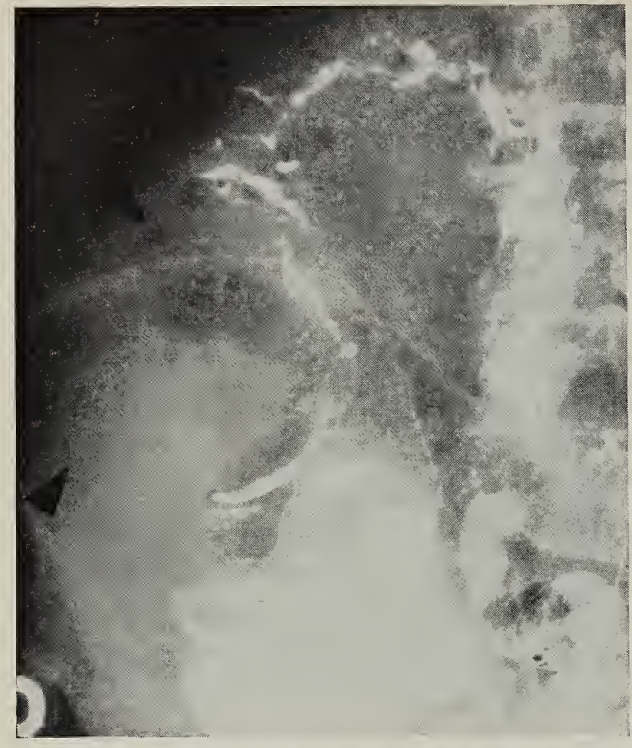

Figure 1.—Film shows appendiceal abscess distorting the right colon. There are well defined gas shadows within the inflammatory mass.

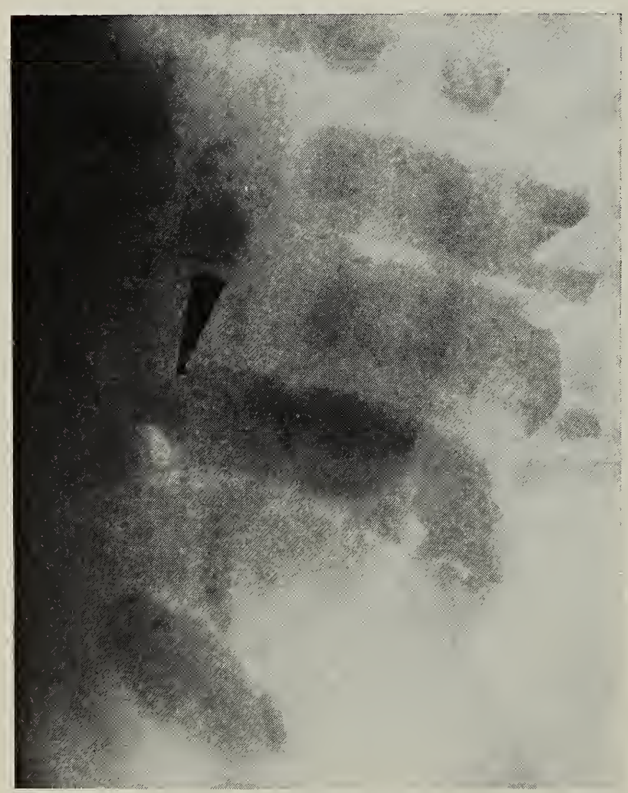

Figure 2: (Case 1).—Roentgenogram showing gas within the appendix. The radiopaque shadows at the tip of the appendix are barium from a previous gastrointestinal study. The film shows numerous gas-filled loops of small bowel projected over the right lower abdomen.

with this roentgen finding. There have been 12 cases reported in which spontaneous pneumoperitoneum was shown radiographically in association with perforation of the appendix. Mentioned as possible sources of intraperitoneal air in the appendiceal lumen were perforation of a gas-containing abscess, either within or outside the appendix, and peritonitis caused by gas-forming organisms. An x-ray film of an appendiceal abscess containing gas is shown in Figure 1.

Report of a Case

A 74-year-old man was admitted to Cottage Hospital in Santa Barbara October 14, 1960 because of generalized cramping abdominal pain. These symptoms increased in severity. The patient had had no bowel movements on the day of admission. He had a history of duodenal ulcer, but the present pain was in no way similar to the previous ulcer pain. On physical examination maximal tenderness was noted in the right lower quadrant of the abdomen. Rebound tenderness was also referred to this area. Bowel tones in the abdomen were diminished. The oral temperature was 101° F. Leukocytes numbered 22,150 per cu mm with the cell differential showing a shift to the left. On roentgen examination a well defined bubble of gas within the appendix was seen (Figure 2).

The pre-operative diagnosis was acute appendicitis. At operation the appendix was found to be gangrenous and a collection of cloudy fluid was noted in the right lower abdomen.

Discussion

There is a paucity of information in the literature concerning the gas-filled appendix. On rare occasions the appendix may normally contain gas. However, in the presence of acute symptoms referable to the abdomen it should raise strong suspicion of gangrenous appendicitis, and a second case is added to the literature to support this assumption.

Santa Monica Hospital, 1250 Sixteenth Street, Santa Monica 90404.

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California Medicine

EDITORIAL

Health Tips

MAN'S INNATE DESIRE to remain healthy, plus his curiosity about his own body and its functioning, make him what newspaper editors would call a "natural" for health articles.

Proof of his willingness to spend time reading articles about human health is found on all sides. Metropolitan newspapers almost without exception publish regular feature columns on health topics. Weekly and monthly magazines regularly number one or more health articles in their contents. Even the American Medical Association follows suit in *Today's Health,* a monthly magazine which is prepared by a staff of physicians and directed to the lay public as an authentic journal of health care topics with an authoritative background.

Until about three years ago, notably missing from the list of publications carrying articles or columns of this kind were the semi-weekly, weekly or semi-monthly newspapers, employee house organs and other publications with an interested but limited readership.

It was with just this group of publications that the California Medical Association's Commission on Community Health Services was concerned several years ago when it voted to establish *Health Tips* as a regular feature to be supplied to publishers.

The prospectus of the Commission was that these articles be sent out each week to publishers who wished to receive them, that the items be medically accurate and presented in a way not to encourage self-medication or self-diagnosis.

Experience in the past three years has proved that many publications are eager to print this material, joining with the physicians of California in this gratis contribution to the health and well-being of the people of our state.

Popularity of these releases has been indicated promptly and directly in several cases, especially where readers are offered supporting material for the asking. For example, a column on first aid offering a chart which could be pasted inside a medicine cabinet drew thousands of requests. A more recent release on the dangers of skateboards—as used by youngsters enthusiastically, by some adults adventurously and by both perilously—was picked up by the press wire services and presented in all parts of the country. Just a month ago in an article on the steps to be taken by parents, by babysitters and by the parents of babysitters, an offer was made to supply some simple check sheets as guidelines to assure good care of children and a full understanding among all parties concerned in this twentieth century occupation. Requests for these sheets are still pouring in.

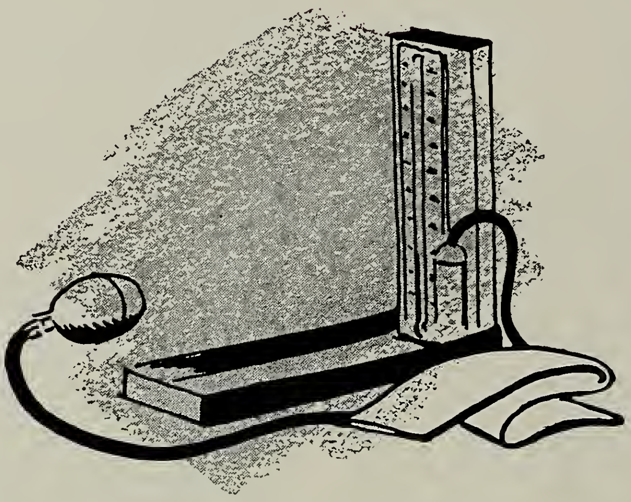
Interestingly, some large house organs regularly use our *Health Tips* columns. In some instances large employers or membership organizations have requested the preparation of "exclusive" columns aimed at their membership or employee groups. Where possible, such requests are met by the Commission on Community Health Services.

The business of preparing *Health Tips* articles is a difficult and painstaking one. Each release must be grounded on the most up-to-date material available. Each must be checked and cross-checked for accuracy and unanimity of opinion in the medical profession. Each must be presented in a style that is readily understandable by the lay reader. Finally, each must provide that the reader be urged to seek professional counsel of a physician when the need is apparent.

This process requires an alert attitude on the part of staff personnel, plus a staff of writers who are aware of their responsibilities. Where competent writers were hard to find at the outset, a group has now been developed who have learned how to combine scientific facts with an easy style of presentation.

Health Tips has established itself as a public service of the California Medical Association. In supplying this service, our association is prosecuting one of its constitutional purposes—"to promote . . . the protection of the public health." And it is doing so in a climate of friendly relations with an important element of the press which it might otherwise not have opportunity to know.

The Commission on Community Health Services is to be congratulated for adopting a good idea, turning out a good product and promoting it with intelligence.



California Medical Association

NOTICES AND REPORTS

CMA Acts on "Medicare"

THE COUNCIL *of the California Medical Association at its meeting August 7, 1965, took two important steps bearing on Public Law 89-97, generally known as the "Medicare Law." One was a statement of policy and the other was creation of a Task Force to represent the CMA's position in whatever actions are taken in the state government of California or in the Federal Government to carry out the provisions of the new legislation.*

THE STATEMENT OF POLICY

1. That the California Medical Association reaffirms its position of endeavoring to assure provision of the highest quality of medical care to all citizens of California.

2. That the California Medical Association, recognizing that the Social Security Amendments of 1965 (Public Law 89-97) is now the law of the United States, offers to meet with agencies of government, institutional providers of care, carriers and other interested parties to assure that implementation of the law—through intent and regulation—will be in the best interests of the highest possible quality of medical care for our patients.

3. That the California Medical Association inform its members, component societies, and the people of this State that as an organization it has neither the right nor the authority to dictate to the individual practicing physician what action he should take with respect to providing medical care under the regulations of Public Law 89-97. Each physician-member of this Association must decide for himself.

4. That the California Medical Association consider diligently the impact of Public Law 89-97 on patient care in coming months and years; and where regulations are imposed which are not in keeping with sound medical practice, the Association will forcefully pursue corrective action, through regulatory changes and/or legislative modifications.

5. That the California Medical Association proposes again to the California State Legislature that State implementation of the new public assistance provisions of Public Law 89-97 contain prepayment mechanisms for all categorical aid programs and that physicians and providers of service be compensated on a "usual, customary and reasonable" basis.

6. That the California Medical Association recommends to the State Legislature that financial benefits accruing to county hospitals through federal matching funds for medical uses in the implementation of Title XIX of Public Law 89-97 in California be used for medical purposes and not diverted into other channels.

7. That the California Medical Association publicize this series of policy statements—through all appropriate channels of communication—to the people of California; to state and federal governmental personnel (both in the executive and legislative branches); to the American Medical Association and its constituent state societies; and to the membership of the California Medical Association.

THE TASK FORCE

The CMA Task Force on Public Law 89-97 was given authority—

(a) To meet with various agencies of state and federal government, prepayment organizations and insurance carriers, other providers of service, and interested parties to assure that Medicine's points of view are forcefully and persuasively presented.

(b) To ask various existing Commissions and Committees to study in depth specific problems and recommend constructive implementation of the law.

(c) To conduct a positively-oriented public and legislative campaign to insure inclusion of the prepayment mechanism and other CMA House of Delegates directions in whatever California legislation is proposed to implement the public assistance provisions of Public Law 89-97.

(d) To work for a maximum of local administration and control and a minimum of centralization.

(e) To bring recommendations to the CMA Council for corrective action—legislative or regulatory—when patient care is threatened.

The Task Force Personnel

The Council approved the following personnel for the Task Force: Ralph C. Teall, Chairman, Sacramento; James C. MacLaggan, San Diego; Bert L. Halter, San Francisco; Roger Isenhour, San Diego; Albert G. Miller, San Mateo; Malcolm C. Todd, Long Beach; Milo A. Youel, San Diego; Dan O. Kilroy, Sacramento; Samuel R. Sherman, San Francisco; John A. Bullis, Los Angeles; Richard S. Wilbur, Palo Alto; Joseph F. Boyle, Los Angeles; Henry V. Eastman, Tustin; H. Dean Hoskins, Oakland, and Donald C. Harrington, Stockton.

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Council Meeting Minutes

Tentative Draft: Minutes of 513th Meeting of the Council, Los Angeles, Airport Marina, August 7, 1965.

The meeting was called to order by chairman Anderson in the Airport Marina, Los Angeles International Airport, on Saturday, August 7, 1965, at 10:00 a.m.

Roll Call

Present were President Teall, President-Elect MacLaggan, Speaker Quinn, Vice-Speaker Telford and Councilors Wilson, Melone, Todd, Taw, Bullock, O'Connor, Rogers, Burnett, R. S. Wilbur, Miller, Fenlon, Kay, Yant, Grunigen and Past President Doyle.

Absent for cause, Editor Dwight L. Wilbur, Secretary Hosmer, Councilors Isenhour, Gooel, Ham, Maguire, Watts, Kaiser and Shaw.

A quorum present and acting.

Present by invitation were Messrs. Thomas, Clancy, Collins, Whelan, Klutch, Clark, Moreillon, Eberlein, Edwards, Bowman, Goldman and Blackley, Doctor Miller, Mmes. Griffith and Redfern and Miss Price of CMA staff; Messrs. Read, Salisbury and Brown of the Public Health League; county executives Scheuber of Alameda-Contra Costa, Rideout of Butte-Glenn, Geisert of Kern, Baker and Rosenthal of Los Angeles, Blankfort of Marin, Colvin of Monterey, Bannister of Orange, Walters of Riverside, Dochterman of Sacramento, Burris of San Diego, Neick of San Francisco, Wood of San Mateo, Marvin of Santa Barbara, Donovan of Santa Clara and Bruce of Tulare; Mr. Paul Ward, Administrator of Health and Welfare Agency; Doctor Malcolm Merrill, Director of the Department of Public Health; J. M. Wedemeyer, Director of the State Department of Social Welfare and Doctor Lester McDonald; Mr. Robert B. Radl of the State Department of Employment, Doctor Robert T. Hewitt of the State Department of Mental Hygiene; Doctors William H. Thompson and T. Eric Reynolds and Messrs. Paolini, Humbert, Heller, Bentley and Babb of California Physicians' Service; Robert Thomas of the California Hospital Association, Doctor William Steinmetz of the California Veterinary Medical Association; Mr. John Pompelli of the American Medical Association; Robert F. Garrick, consultant; Doctors Dan O. Kilroy, Warren L. Bostick, Joseph Turner, J. Lafe Ludwig, Eugene Hoffman and others.

1. *Minutes for Approval*

On motion duly made and seconded the minutes of the 512th meeting of the Council held June 12, 1965, were approved after the notation that there was a typographical error under the Scientific Board report dealing with House of Delegates' resolution on hemodialysis centers. The resolution number should read #49-65 rather than #39-65, as printed in the minutes of June 12.

2. *Membership*

(a) A report of membership as of August 4, 1965, was presented and ordered filed.

(b) On motion duly made and seconded, 258 delinquent members whose dues had been paid subsequent to the preceding meeting were voted reinstatement.

(c) On motion duly made and seconded in each instance, 15 applicants were voted into Associate Membership. These were: Edwin Arthur Balcer, Kathryn M. Smick, Carl Louis Smith, Alameda-Contra Costa County; James T. Duncan, Kern County; Wm. Warren Roe, Jr., Claire M. Stiles, Betti Jo Warren, Los Angeles County; Irving Richard Lyman, Mendocino-Lake County; Salvador Macis, San Bernardino County; Harold Wm. March, Sean O'Reilly, San Francisco County; Haruko Harry Kawagoe, Mason Walter Robison, San Luis Obispo County; Elmer W. Gilbert, Tulare County; Alan J. Kringle, Santa Clara County.

(d) On motion duly made and seconded in each instance, three applicants were voted Retired Membership. These were: Anita E. Faverman, Alameda-Contra Costa County; Paul F. Thuresson, Riverside County; Henry L. Gardner, San Francisco County.

(e) On motion duly made and seconded in each instance, 11 members were voted a reduction of dues because of postgraduate training or prolonged illness.

3. *Honorary Degree for Doctor Edward B. Shaw*

Chairman Anderson announced that the University of California had conferred upon Doctor Edward B. Shaw, chairman of our Scientific Board, an honorary LLD.

ACTION: Voted to congratulate Doctor Edward B. Shaw and to appoint him "honorary legal counsel" to the California Medical Association.

4. *1966 Conference of Component Society Officers*

Doctor L. Morgan Boyers, ad hoc planning committee chairman, reported on the plans for the 1966 Conference of Component Society Officers, to be held at the Airport Marina Hotel, Los Angeles, January 15, 1966.

ACTION: Council approved the format and plans of the committee and asked it to proceed.

In addition, Doctor Boyers reported to the Council that the planning committee had heard discussion on the problems of judicial council proceedings and appeals at the local and state level. The committee suggested that this might be subject matter for a conference to be held during the 1966 Annual Session. The suggestion, with consent of the Council, was passed on to the Commission on Professional Welfare.

5. *Report of the President*

President Teall reported that the California Medical Education & Research Foundation was still considering the matter of funds to support continuing education but that action on this would have to be postponed until some decision could be made about the CMA commitment to the California College of Medicine.

He also brought to the attention of the Council correspondence from Doctor Thomas J. Gray, Director of Student Health Service, San Jose State College, regarding the California State College Health Service study.

President Teall reviewed the CMA and AMA positions and actions on AB 760 in the California General Session, AB 2 in the Special Session and HR 6675 in Congress.

6. *Committee for Emergency Action*

President Teall reported on deliberations of the Emergency Action Committee meeting of Friday, August 6. The Emergency Action Committee proposed to the Council that two steps be taken with regard to Public Law 89-97 (HR 6675), as follows:

1. Formulation of a statement of policy by this Association, and

2. Establishment of a special CMA Task Force to give its sole attention to the implications of Public Law 89-97.

ACTION: The Council voted an amended statement of policy on Public Law 89-97 which follows.

1. That the California Medical Association reaffirms its position of endeavoring to assure provision of the highest quality of medical care to all citizens of California.

2. That the California Medical Association, recognizing that the Social Security Amendments of 1965 (Public Law 89-97) is now the law of the United States, offers to meet with agencies of government, institutional providers of care, carriers and other interested parties to assure that implementation of the law—through intent and regulation—will be in the best interests of the highest possible quality of medical care for our patients.

3. That the California Medical Association inform its members, component societies, and the people of this State that as an organization it has neither the right nor the authority to dictate to the individual practicing physician what action he should take with respect to providing medical care under the regulations of Public Law 89-97. Each physician-member of this Association must decide for himself.

4. That the California Medical Association consider diligently the impact of Public Law 89-97 on patient care in coming months and years; and where regulations are imposed which are not in keeping with sound medical practice, the Association will forcefully pursue corrective action, through regulatory changes and/or legislative modifications.

5. That the California Medical Association proposes again to the California State Legislature that State implementation of the new public assistance provisions of Public Law 89-97 contain prepayment mechanisms for all categorical aid programs and that physicians and providers of service be compensated on a "usual, customary and reasonable" basis.

6. That the California Medical Association recommends to the State Legislature that financial benefits accruing to county hospitals through federal matching funds for medical uses in the implementation of Title XIX of Public Law 89-97 in California be used for medical purposes and not diverted into other channels.

7. That the California Medical Association publicize this series of policy statements—through all appropriate channels of communication—to the people of California; to state and federal governmental personnel (both in the executive and legislative branches); to the American Medical Association and its constituent state societies; and to the membership of the California Medical Association.

ACTION: The Council adopted the above statement.

ACTION: The Council voted to establish a special "CMA Task Force on Public Law 89-97" to be charged with the responsibility of both state programs and positive actions regarding this new law, utilizing to the greatest extent possible existing commissions and committees to implement specific actions. Such a Task Force was given authority—

(a) To meet with various agencies of state and federal government, prepayment organizations and insurance carriers, other providers of service, and interested parties to assure that Medicine's points of view are forcefully and persuasively presented.

(b) To ask various existing Commissions and Committees to study in depth specific problems and recommend constructive implementation of the law.

(c) To conduct a positively-oriented public and legislative campaign to insure inclusion of the prepayment mechanism and other CMA House of Delegates directions in whatever California legislation is proposed to implement the public assistance provisions of Public Law 89-97.

(d) To work for a maximum of local administration and control and a minimum of centralization.

(e) To bring recommendations to the CMA Council for corrective action—legislative or regulatory—when patient care is threatened.

ACTION: The Council also asked the CMA Executive Director to establish a parallel committee of staff personnel to assist the Task Force in the implementation of its responsibilities and that the Executive Director use county executive secretaries as resource personnel.

It was recommended that the Committee on Committees make nominations for the special Task Force on Public Law 89-97 and report back to the Council later in the day.

7. *Committee on Committees*

Doctor James C. MacLaggan, Chairman, offered the following nominations:

(a) *Sub-Committee on Venereal Disease* — It was recommended that a new sub-committee be formed under the Committee on Public Health, consisting of Doctors Thomas E. Jones of Fullerton, Willard M. Meininger of Sacramento, Horace Sharrocks of Sebastopol and Walter E. Batchelder of San Mateo.

(b) *Interagency Council on TB*—It was recommended that Corwin Hinshaw of San Francisco, be designated as a CMA representative.

(c) *Medical Review and Advisory Committee*—Carl Goetsch of Berkeley vice Louis S. Baer.

(d) *Liaison Committee to State Bar of California*—Robert McNeil of Los Angeles vice Harold E. Wilkins.

(e) *Committee on Federal Medical Care Programs*—Ralph Hoffman of San Diego vice Bruce H. Marshall.

(f) *Council ad hoc Committee on Libraries*—It is recommended that a new ad hoc committee be formed, composed of Albert Miller, San Mateo, Chairman; Roger Isenhour of San Diego, James Yant of Sacramento and Franklin Ham of Van Nuys.

(g) *Referendum and Petition* — It is recommended that the study on referendum and petition requested by the House of Delegates (Resolution 20-65) be referred to the House ad hoc committee which has already been named to study representation and councilor districts. (John Bullis, Los Angeles, Chairman). It is further recommended that this House committee report back to the Council by January 1966.

(h) *Resolution 19-65 (Re: Commission on Economics)*—It is recommended that the Bureau of Research & Planning and the Commission on Medical Services select three members each to meet with the author of this resolution and report back to the Council. Chairman of the Commission on Medical Services should be chairman of this six-man group.

(i) *Committee on Paramedical Personnel*—It is recommended that the chairman of the Liaison Committee to CMAA be made a member of this committee.

(j) *Liaison Committee to CHA*—It is recommended that the special Liaison Committee to CHA, as approved at the last meeting, not be activated. The responsibilities that would have gone to such a committee should be assigned to the Commission on Hospital Affairs.

(k) *Scientific Board*—It is recommended that Hobart Kelley of Riverside and J. Blair Pace of Oceanside be appointed to replace Doctors James Moore and A. J. Franzi, resigned.

(l) *Medical Staff Survey Committee* — Add James L. Rhee of Oakland.

(m) *Advisory Committee to Project for Medical Follow-up of Selective Service Rejectees - State Department of Public Health*—Alfred F. Kandlbinder of Monterey.

(n) *Hospital Advisory Board*—Jack Chamber of Sacramento and Paul Doehring, Glendale.

(o) *Hospital Advisory Council*—Richard Taw of Los Angeles.

(p) *CHIPS* — State Department of Public Health Advisory Committee: James C. MacLaggan of San Diego and Glenn A. Pope of Sacramento.

(q) *Council Task Force on Public Law 89-97*—Ralph C. Teall, Chairman, Sacramento; James C. MacLaggan, San Diego; Bert L. Halter, San Francisco; Roger Isenhour, San Diego; Albert G. Miller, San Mateo; Malcolm C. Todd, Long Beach; Milo A. Youel, San Diego; Dan O. Kilroy, Sacramento; Samuel R. Sherman, San Francisco; John A. Bullis, Los Angeles and Richard S. Wilbur, Palo Alto.

After consideration, the Council suggested four additional nominees to the Task Force on Public Law 89-97, as follows: Joseph F. Boyle, Los Angeles; Henry V. Eastman, Tustin; H. Dean Hoskins, Oakland and Donald C. Harrington, Stockton.

(r) *Council ad hoc Committee on the DeBakey Commission Report*—James C. MacLaggan, San Diego, Chairman; Sanford E. Feldman, San Francisco; Malcolm S. M. Watts, San Francisco; Carl Goetsch, Berkeley; James Martin, Sacramento; Ralph W. Burnett, Bakersfield; Kenneth Jennings, Santa Barbara; John T. Saidy, San Mateo; Roger O. Egeberg, Los Angeles; Francis E. West, San Diego; Omer Wheeler, Riverside; Justin J. Stein, Los Angeles; George Griffith, Los Angeles; Robert Westphal, Modesto; and Richard Taw, Los Angeles.

ACTION: Council voted approval of the above recommendations.

Doctor MacLaggan further recommended that the two committees previously concerned with the Kerr-Mills and the Casey program be dissolved, since the responsibilities of these two committees will become part of the province of the new Task Force on Public Law 89-97.

ACTION: Voted to dismiss, with thanks, the Committee on California Plan for the Aged and the ad hoc Committee on Kerr-Mills.

8. *AMA Meeting With President Johnson*

Chairman Anderson read appropriate paragraphs from a letter to him from Doctor Samuel Sherman regarding an AMA special meeting with President Johnson on July 29, 1965, on the Medicare Proposal.

8a. *AMA Delegation*

Doctor J. Lafe Ludwig, chairman of the California delegation, reported on the recent AMA House of Delegates meeting in New York City and paid tribute to the seven California delegates who served on reference committees and to California's leadership on several resolutions.

Doctor Ludwig also reported that the delegation agreed to start its advocacy for the election of Doctor Dwight L. Wilbur as President-Elect of the AMA in 1967.

9. *State Health and Welfare Agency*

Mr. Paul Ward, Administrator of the State Health and Welfare Agency, presented to the Council the administration's views on what had happened with AB 760 during the regular session of the Legislature and what he envisioned as to the proposals that would be made in the special session in October. Mr. Ward said the main problem during the general session was the debate between state government and county government as to the allocation of certain funds for the medical care of indigent and medically indigent persons. He suggested that the bill which will be proposed in October should include:

(a) Comprehensive coverage for all of the categorical aid recipients under Title XIX of P. L. 89-97.

(b) That the additional federal dollars available under Title XIX or produced by it be used for medical purposes, and

(c) That the prepayment or insurance principle should be included.

ACTION: The Council adopted point #2 above and included it as part of the policy statement on Public Law 89-97.

10. *State Department of Social Welfare*

Mr. J. M. Wedemeyer, director of the department, noted that the main welfare concept embodied in AB 760 was to redesign completely the traditional approach to welfare medical care. The concepts in 760, he said, would allow welfare patients to be in the main stream of medical care and give them the incentive to return to general society.

11. *State Department of Public Health*

Doctor Malcolm Merrill, department director, expressed appreciation to the CMA for its assistance on health legislation and the departmental budget during the recent session of the Legislature. He itemized those new and additional responsibilities which his department has been assigned as a result of the legislative session.

12. *State Department of Mental Hygiene*

Doctor Robert T. Hewitt, deputy director, informed the Council that an amendment to the Short-Doyle Act provides that differences on policy matters existing between the director of the State Department of Mental Hygiene and the Conference of County Mental Health Officers will be submitted to arbitration. He also noted that the CMA was being asked to cooperate with the department in Senate Resolution 166, which is to study staff needs of state mental institutions.

13. *California College of Medicine*

Dean Warren L. Bostick informed the Council that the second phase of the College's affiliation with the University of California would probably occur about October 1, thereby making the College campus No. 10 of the University of California and would change somewhat the financial status of the institution.

14. *California Veterinary Medical Association*

Doctor William Steinmetz, President, expressed appreciation to the Council for its interest in the problems of veterinary medicine. He emphasized that his association was concerned with many problems similar to those encountered by practicing physicians, such as research, continuing education, recruitment, etc. He expressed pleasure at having the opportunity to meet in late September with the CMA Committee on Other Professions and to explore further mutual programs.

15. *California Physicians' Service*

Doctor William Thompson, chairman of the CPS Board, related the plans of CPS to qualify as a carrier under Part B of P.L. 89-97.

ACTION: Voted to direct CPS, on behalf of the doctors of California, to qualify itself as a carrier under Public Law 89-97.

16. *State Board of Medical Examiners*

Doctor Donald Abbott, President, emphasized that the physicians who are ultimately selected to serve on the regional committees under the State Board of Medical Examiners will be required to spend approximately five to six weeks a year of their time hearing cases. He asked for the continued cooperation of CMA in the implementation of Senate Bills 400 through 405. He emphasized the Board's determination to proceed slowly and cautiously in interpreting and applying the new provisions of the Medical Practice Act.

17. *Bureau of Research & Planning*

Mr. Murray Klutch, research director, reported for Doctor Sherman, recommending CMA development of guidelines for establishing in-hospital medical staff utilization committees.

ACTION: Voted to refer this subject to the newly created Task Force on P.L. 89-97 and the Commission on Hospital Affairs.

Permission was asked to distribute to county societies its study on Non-Membership in LACMA; to ask the Commission on Communications to use the study in plans to make county society and CMA membership more attractive; to ask the Commission on Communications to evaluate the results of these efforts.

ACTION: To approve the recommendations of the Bureau with the stipulation that the report contain a reference indicating a limitation with regard to the question of dues required by the state and national associations, as suggested by Councilor O'Connor.

It was recommended that the CMA participate actively in various planning activities in California which relate to the President's Commission on Heart Disease, Cancer and Stroke.

ACTION: Voted to accept this proposal and refer it to the ad hoc Committee on the DeBakey Commission Report.

The Bureau requested permission to distribute the Report of the Role of Medicine in Society to a list of organizations and individuals outside of California which had asked for copies.

ACTION: Voted to grant permission to the Bureau to distribute the report, with the exception of the American Psychoanalytic Association. Mr. Klutch was asked to get further information on this group and report back to the Council.

18. *Committee on Legislation*

Doctor Dan O. Kilroy referred briefly to a detailed written report of the Committee on Legislation regarding the results of the recent general session. He noted that the Assembly interim committee hearings this time will be devoted more to subject matter than to specific bills which were assigned to interim study.

Doctor Kilroy also asked the Council to send the CMA policy statement on Public Law 89-97 to legislators and members of the executive branch of state government.

ACTION: It was voted to send statement as requested above, and to California Senators and Representatives in Congress.

Mr. Ben Read, Executive Secretary of the Public Health League, announced to the Council that the Sacramento office will be open year-round.

19. *Liaison Committee to CPS*

Mr. Thomas reported for the CPS Liaison Committee and asked for approval of the committee recommendations regarding House of Delegates resolution #1-65 on CPS payments; payments for House staffs of teaching hospitals; laboratory clinical profiles and a request to the Committee on Fees to include in the RVS a description and unit value for the drawing of blood for laboratory examination.

ACTION: The four items of the August 7 report of the CPS Liaison Committee were approved.

20. *Workmen's Compensation*

Doctor Anderson reported on the activities of the ad hoc Committee on Workmen's Compensation and asked that the committee be continued to work with the Division of Industrial Accidents on the implementation of the new legislation.

ACTION: Council voted to continue the ad hoc Committee on Workmen's Compensation.

21. *Medical Discipline*

Doctor Anderson presented to the Council a mechanism for CMA coordination of county society nominations for the five regional committees under the State Board of Medical Examiners.

ACTION: Voted to approve the concept of CMA coordination of nominations. A county society will be invited to submit one or more nominations on the basis roughly of the physician population in the area.

22. *Commission on Medical Services*

Council permission was sought for the approval of a standardized claim form developed by the Health Insurance Council.

ACTION: Voted to approve standardized claim form as noted in the commission report.

23. *Commission on Community Health Services*

Doctor Harold Kay reported that a new Health Tip on baby sitting had generated over 60,000 requests in the first week of distribution.

He also asked for Council guidance as to what action should be taken on cooperation with the Dental Associations in a fluoridation campaign (a survey of county societies indicated that less than 25 per cent were interested in a fluoridation campaign).

ACTION: Voted to reaffirm the 1962 House of Delegates position on fluoridation, which, in essence, said that the CMA would follow the lead of the two Dental Associations in any campaign to introduce fluorides into public drinking water facilities.

24. *Commission on Communications*

Doctor Todd reported on several activities of the Commission. He asked for permission to publish a CMA Activities and Personnel Directory on a semi-annual basis.

ACTION: Permission granted to publish the directory.

Report was made on the participation of the CMA in the California Interagency Council on Smoking and Health.

ACTION: Voted to have Doctor Todd send a letter to the Chairman of the Interagency Council emphasizing that the CMA's participation originally was for educational and publicity purposes and that the Interagency Council should not be involved in sponsoring or endorsing state legislation independently. Any Interagency Council involvement in legislative matters must be brought to the CMA Council for policy consideration.

Doctor Todd asked for approval for two representatives of the Commission to attend the AMA Public Relations Institute in Chicago August 19-20.

ACTION: Permission granted.

Permission was requested to publish a bimonthly Bulletin directed toward chiefs of staffs in California hospitals.

***ACTION:* Voted to publish the bulletin on a one-year trial basis.**

Doctor Todd asked for Council approval to produce a supplemental 1965 Annual Report in addition to the Annual Reports Bulletin.

***ACTION:* Permission granted for a one-time trial.**

Doctor Todd asked for Council approval for a communications work-shop to be held in the fall of 1966.

***ACTION:* Voted to refer the recommendation back to the Commission on Communications with the suggestion that the workshop idea be included in a future Component Society Officers Conference.**

25. *Finance Committee*

President Teall asked for an initial allocation of $70,000 of unbudgeted funds to finance the expenses of the newly created Task Force on Public Law 89-97.

Doctor Harold Kay, Finance Committee chairman, noted that the Finance Committee had approved initial funds.

***ACTION:* Voted to approve an initial allocation of $70,000 to the Task Force, with the understanding that a more detailed budget would be presented at a later meeting of the Council.**

26. *Commission on Hospital Affairs*

Doctor Bert Halter, commission chairman, asked the Council for permission to establish suggested guidelines for utilization and admissions committees. He suggested that the utilization committee might have to establish a "rolling evaluation" concept in utilization practices.

***ACTION:* Voted to ask the Commission on Hospital Affairs to establish guidelines for utilization committees and to stimulate medical staff interest in the subject.**

27. *Commission on Professional Welfare*

Doctor Yant and Mr. Whelan presented a draft of model medical staff bylaws.

***ACTION:* Model staff bylaws approved for distribution.**

28. *Commission on Allied Health Professions*

Doctor Forest Grunigen, commission chairman, recommended that the Committee on Committees select a representative from the Scientific Board to act as a liaison person to the California Veterinary Medical Association.

***ACTION:* Approved referral to the Committee on Committees.**

29. *Two-Day Council Meeting*

Discussion was held regarding the advisability of having a two-day Council session in October on various items of concern.

***ACTION:* Voted to have a two-day Council meeting October 30-31, 1965, with Saturday to cover the regular agenda and Sunday to be in executive session.**

Adjournment

There being no further business to come before the meeting, it was adjourned at 4:45 p.m.

CARL E. ANDERSON, M.D., *Chairman*
FRANK CLARK, *Acting Secretary*

In Memoriam

Ames, Julian G., Glendora. Died May 13, 1965, in San Marino, aged 66, of a coronary. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1931. Licensed in California in 1931. M.D. degree from California College of Medicine, 1962. Doctor Ames was a member of the Los Angeles County Medical Association.

◆

Baisinger, Leo Fenimore, Bakersfield. Died August 15, 1965, aged 55, of injuries received in an automobile accident. Graduate of the University of Nebraska College of Medicine, Omaha, 1934. Licensed in California in 1938. Doctor Baisinger was a member of the Kern County Medical Society.

◆

Beem, Theodore Myrle, North Hollywood. Died August 7, 1965, in Burbank, aged 68, of heart disease. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1938. Licensed in California in 1938. Doctor Beem was a member of the Los Angeles County Medical Association.

◆

Davis, Fred Jay, Sr., Susanville. Died August 19, 1965, aged 82, of a massive coronary. Graduate of Cooper Medical College, San Francisco, 1907. Licensed in California in 1907. Doctor Davis was a member of the Lassen County Medical Society.

◆

Delprat, G. Daniel, San Francisco. Died August 23, 1965, in San Francisco, aged 68. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1922. Licensed in California in 1922. Doctor Delprat was a member of the San Francisco Medical Society.

◆

Galgiani, John Veiller, San Francisco. Died August 22, 1965, in San Francisco, aged 53. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1938. Licensed in California in 1938. Doctor Galgiani was a member of the San Francisco Medical Society.

◆

Handgriff, Moritz, Santa Monica. Died August 28, 1965, in Santa Monica, aged 71, of bronchial pneumonia. Graduate of Medizinische Fakultät der Universität, Wein, Austria, 1921. Licensed in California in 1941. Doctor Handgriff was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Jones, Richard Barr, Modesto. Died July 31, 1965, in Modesto, aged 62, of carcinoma of the lung. Graduate of the University of Cincinnati College of Medicine, Ohio, 1927. Licensed in California in 1931. Doctor Jones was an associate member of the Stanislaus County Medical Society.

◆

Jordan, Robert Henry, Napa. Died August 14, 1965, in Napa, aged 45, of injuries received in an automobile accident. Graduate of the University of Virginia School of Medicine, Charlottesville, 1953. Licensed in California in 1958. Doctor Jordan was a member of the Napa County Medical Society.

◆

Kempler, Samuel Lawrence (S. Lawrence), Sacramento. Died August 23, 1965, in San Francisco, aged 56. Graduate of the University of Rochester School of Medicine and Dentistry, New York, 1936. Licensed in California in 1946. Doctor Kempler was a member of the Sacramento County Medical Society.

◆

King, Robert Wade, Oakland. Died July 29, 1965, in Walnut Creek, aged 59, of heart disease. Graduate of Northwestern University Medical School, Chicago, Illinois, 1934. Licensed in California in 1934. Doctor King was a member of the Alameda-Contra Costa Medical Association.

◆

McGinn, Walter E. Jr., Los Angeles. Died July 26, 1965, in Virginia, aged 42, of injuries received in an automobile accident. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1957. Licensed in California in 1958. M.D. degree from California College of Medicine, 1962. Doctor McGinn was a member of the Forty First Medical Society.

◆

Newell, Robert Reid, San Francisco. Died August 27, 1965, in San Francisco, aged 73, of cerebral vascular accident. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1916. Licensed in California in 1916. Doctor Newell was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

◆

Orlando, William Fazio, Northridge. Died August 16, 1965, in San Fernando, aged 56. Graduate of Chicago Medical School, Illinois, 1938. Licensed in California in 1950. Doctor Orlando was a member of the Los Angeles County Medical Association.

◆

Sharp, John Chester, Pacific Grove. Died August 4, 1965, in Monterey, aged 65. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1932. Doctor Sharp was a member of the Monterey County Medical Society.

◆

Spivek, Mandel Lawrence, Beverly Hills. Died August 9, 1965, in Pinedale, Wyoming, aged 62, of heart disease. Graduate of Rush Medical College, Chicago, Illinois, 1929. Licensed in California in 1946. Doctor Spivek was a member of the Los Angeles County Medical Association.

◆

Weitemier, Stanley Allen, Orangevale. Died July 28, 1965, in Folsom, aged 40. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1952. Licensed in California in 1953. M.D. degree from California College of Medicine, 1962. Doctor Weitemier was a member of the Forty First Medical Society.

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PLANS FOR THE 1966 ANNUAL SCIENTIFIC ASSEMBLY ARE NOW IN PROGRESS

PLAN **YOUR** CONTRIBUTION TO THE PROGRAM **TODAY**

PUBLIC HEALTH REPORT

MALCOLM H. MERRILL, M.D., M.P.H.
Director, State Department of Public Health

In cooperation with the San Joaquin Local Health District and the Stockton Unified School District the State Department of Public Health has initiated a demonstration project to assist local physicians and schools by providing diagnostic and consultative services for children handicapped by learning disorders caused by "minimal cerebral dysfunction."

This term is now used to designate the conditions formerly referred to as "minimal brain damage," "neurologically handicapped," certain learning and perceptual disabilities and the "hyperkinetic behavior syndrome."

It is estimated there are 70 to 100 such neurologically impaired school children in the Stockton area who are in need of diagnosis and special management. Many more children who have mild to moderate degrees of this syndrome can be taught in regular classes, but would benefit from early and accurate identification of their individual learning disorders so that the most suitable educational techniques could be applied.

Project services provided include pediatric, neurological, electroencephalographic, social work and psychological evaluations. The pediatric evaluations are done by local specialists; the neurological consultations are provided by visiting neurologists from San Francisco. The psychological evaluations are provided by psychologists of the Stockton Unified School District.

The child's private physician participates in the case conference that is held after these evaluations and assists in formulating the diagnosis and recommendations for the child's medical, educational and social management. Reports and recommendations are made available to the child's physician for use in his supervision of the child's medical care and to the school's Admission Committee in its determination of a child's eligibity for the special classes, disabilities teachers, or home instruction.

Besides providing local physicians with a resource of outpatient diagnostic and consultative neurological services by a team of specialists, the project is exploring learning disabilities syndromes, the nature and extent of these problems among children of school age, and investigating procedures for improving the screening, diagnosis and the medical and educational management of such handicapped children.

Funds to support this three-year project have been awarded to the Department's Bureau of Chronic Diseases by the Neurological and Sensory Disease Program of the U.S. Public Health Service.

* * *

The need to have a patient with congestive heart failure adhere daily to his treatment program which he may have to continue for the duration of his life is one of the major areas of concern in providing total care.

As a way of assisting the patient, the department's Heart Disease Control program is developing a programed text, utilizing the programed instruction teaching method, to be used by the patient before his discharge from the hospital.

The text is to be ready for use by patients this October. Those responsible for the program are now considering hospital locations and welcome information regarding potential hospital sites for demonstration studies. If interested, please contact the department's Bureau of Chronic Diseases, 2000 Hearst Street, Berkeley.

* * *

The department's Bureau of Occupational Health currently is conducting a comprehensive study of the effects of heat, noise and dust on the health of heavy construction equipment operators.

The study is the first of this type undertaken in the construction industry and is part of the department's continuing program aimed at the prevention of work-induced disease and disability in California's labor force.

Cooperating in this work are the U.S. Public Health Service, the Operating Engineers Union and a number of construction contractors.

The survey will include canal, freeway and other construction projects in the Sacramento and San Joaquin Valleys. The survey team, made up of physicians and engineers, will examine a total of 150 men and their jobs for 30 days.

NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

The Institute for Comprehensive Medicine will sponsor a symposium on "Psychotherapy and Psychotropic Drugs for the Anxious and Depressed Patient" to be held October 29 at the Statler-Hilton, Los Angeles, from 12 noon to 5 p.m. Authorities from various disciplines of psychiatry, medicine and dentistry will discuss the use of psychotropic drugs, the role of the general practitioner in the psychotherapeutic handling of disturbed patients, management of the tense dental patient, and the comprehensive approach relative to medical problems.

Further information may be obtained from the Institute for Comprehensive Medicine at 9735 Wilshire Boulevard, Beverly Hills 90212.

* * *

The 18th Annual Midwinter Radiological Conference, sponsored by the **Los Angeles Radiological Society,** will be held at the International Hotel (adjacent to Los Angeles International Airport), January 29-30, 1966.

The program will include the following speakers: Dr. J. H. Middlemiss, director of radiology, Bristol Royal Hospital, Royal Infirmary Branch, Bristol, England; Dr. Philip J. Hodes, chairman, department of radiology, Jefferson Medical College Hospital, Philadelphia; Dr. Orliss Wildermuth, director of the Tumor Institute of the Swedish Hospital, Seattle; Dr. Manuel Viamonte, Jr., associate professor of radiology, University of Miami School of Medicine, Miami; Professor Solve Welin, director of roentgen diagnostic, Allmanna-Sjukhus, Malmo, Sweden.

* * *

Dr. Grant Gwinup has been appointed associate professor of medicine and head of the Section of Endocrinology and Metabolism at the **California College of Medicine,** which recently became an affiliate of the University of California. Dr. Gwinup was formerly an assistant professor at the Ohio State University Health Center.

* * *

Dr. Arthur E. DeNio, Long Beach, has been elected to a one-year term as a member of the board of directors of the **Flying Physicians Association.** Dr. DeNio is the immediate past president of the organization's California chapter which has more than 200 members.

SAN FRANCISCO

Dr. Dwight L. Wilbur, San Francisco, has been appointed a member of the executive committee which was formed by President Lyndon B. Johnson to plan a **White House Conference on Health** to be held later this fall.

The conference was called to carry out the President's proposal to "bring together the best minds and the boldest ideas to deal with the pressing health needs of the nation."

Cooperation with a program to induce persons rejected by the armed forces to obtain needed medical care in their civilian surroundings was urged by Dr. Ralph C. Teall, president of the California Medical Association, in a letter to presidents and secretaries of component medical societies of the state association.

"The State of California through its Department of Public Health has contracted with the Department of Health, Education and Welfare of the United States," Dr. Teall explained, "to conduct a follow-up program on military medical rejectees in an effort to ensure that needed medical care is obtained. In order to pursue this program the cooperation of practicing physicians is requested.

"When a draftee has been rejected for medical reasons," the letter continued, "he is interviewed by personnel of the follow-up program at the examining station and informed why he has been rejected. If he is considered to need medical care and follow-up, he is so advised and is asked to authorize the use of his medical records for follow-up. The name of his personal physician and cause of rejection is sent to the health department in his home county or city and the follow-up is started.

"The rejectee is urged to obtain indicated treatment from his own physician whenever possible. He is followed in an effort to make sure that necessary care is obtained by contacting the physician to whom he is referred. Each rejectee enters this program on a voluntary basis; for this reason cooperation of the private physician is essential. All records are confidential. After an appropriate period of time physicians are again contacted to learn the progress of the rejectee, and the case is closed and reported to the State Department of Public Health."

Dr. Teall asked component societies to urge their members to cooperate in this program. He suggested that any inquiries or questions be directed to George V. Potter, M.D., Head, Armed Forces Medical Rejectees Health Referral Service, State Department of Public Health, 2151 Berkeley Way, Berkeley, California 94704.

GENERAL

The American College of Chest Physicians has announced the opening of competition for the three cash awards it gives annually for the best essay prepared by undergraduate medical students on any phase of the diagnosis or treatment of chest diseases. The first prize will be $500, second prize $300 and third prize $200. Each winner will also receive a certificate of merit.

Winners will be announced at the 32nd Annual Meeting of the American College of Chest Physicians, to be held in Chicago June 23-27, 1966.

Official application forms, sample copies of the journal, and additional information may be secured by writing Mr. Murray Kornfeld, executive director of the organization, American College of Chest Physicians, 112 East Chestnut Street, Chicago.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts
for Postgraduate Course Information

CMA: **California Medical Association**
For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. PRospect 6-9400, Ext. 68.

LLU: **Loma Linda University**
For information contact: W. F. Norwood, Ph.D., Assistant Dean and Chairman, Division of Continuing Education, Loma Linda University School of Medicine, 1720 Brooklyn Ave., Los Angeles 90033, ANgeles 9-7241, Ext. 214.

PRES. MED. CTR. **Presbyterian Medical Center**
For information contact: Arthur Selzer, M.D., chairman, Education Committee, Presbyterian Medical Center, Clay and Webster Streets, San Francisco 94115. WEst 1-8000.

UCLA: **University of California at Los Angeles**
For information contact: Charles R. Smart, M.D., Assistant Director, Continuing Education in Medicine and Health Sciences, UCLA Medical Center, Los Angeles, 90024, 478-9711, Ext. 2114.

UCSF: **University of California, San Francisco**
For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, University of California Medical Center, Room 565-U, San Francisco 94122, 666-1692.

USC: **University of Southern California**
For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, USC School of Medicine, 2025 Zonal Ave., Los Angeles 90033, 90033, CApital 5-1511, Ext. 300.

STAN: **Stanford University**
For information contact: Roy Cohn, M.D., Associate Dean for Graduate Affairs, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto, DAvenport 1-1200.

OCTOBER

October 15-16—**Central Nervous System Infections.** UCSF. Friday-Saturday.

October 15-16—**Logical Glaucoma Therapy.** UCSF. Friday-Saturday. 14 hours. $50.

October 16—**Imperial County Medical Society Program on Emergency Room Treatment.** Barbara Worth Country Club. Saturday. 8 hours. Contact: Imperial County Medical Society, El Centro.

October 18-22—**Pediatric Allergy.** UCSF. Monday-Friday. 27 hours. $125.

October 19-November 23—**Neuropsychiatry in Daily Practice.** Agnews State Hospital, San Jose. UCSF. Tuesdays. 12 hours. $10.

October 20—**Newborn Infant Care.** USC. Wednesday. 8 hours. $25.

October 20-April 20—**Basic Science Course in Ophthalmology.** UCLA. Wednesdays. Lecture: 49 hours, Lab: 31½ hours. $175 for full course.

October 22-24—**California Society of Internal Medicine Annual Meeting.** Hotel Del Coronado, Coronado. Friday-Sunday. Contact: Nancy V. Louw, executive secretary, California Society of Internal Medicine, 350 Post Street, San Francisco 94108.

October 23—**Endocrine and Metabolic Disorders.** UCSF at Childrens Hospital, San Francisco, Saturday. 7½ hours. $15.

October 23—**Obstetrics and Gynecology Annual Fall Seminar.** Auditorium of the Santa Clara County Administration Building, 70 West Hedding Street, San Jose. Saturday from 8:30 a.m. to 4:30 p.m. Contact: Howard W. Christopher, M.D., secretary, Shufelt Society of Santa Clara County, 621 E. Campbell Ave., Campbell.

October 23-24—**Practical Management of Surgical Problems.** UCSF at Franklin Hospital, San Francisco. Saturday-Sunday. 10¾ hours. $30.

October 24-27—**California Academy of General Practice Annual Scientific Assembly.** Statler Hotel, Los Angeles. Sunday-Wednesday. 13 hours. Contact: Mr. William W. Rogers, executive secretary, California Academy of General Practice, 9 First Street, Room 900, San Francisco.

October 27-29—**American Thoracic Society Postgraduate Course on the Evaluation of Pulmonary Function.** Stanford University School of Medicine, Palo Alto. Wednesday-Friday. 24 hours. $75. $50 for ATS members. Contact: Rudy Glover, Tuberculosis and Health Association of California, 424 Pendleton Way, Oakland.

October 28-31—**Pacific Coast Fertility Society Annual Meeting.** Sahara Hotel, Las Vegas. Thursday-Sunday. Contact: Gregory Smith, M.D., 909 Hyde Street, San Francisco 94109.

October 29—**Kern County General Hospital Postgraduate Conference.** Kern County General Hospital, 1830 Flower Street, Bakersfield. Friday. 8 hours. Contact: George A. Paulsen, M.D., chairman, Postgraduate Conference Committee, Kern County General Hospital.

October 29-30—**Arthritis in Practice.** UCSF. Friday-Saturday. 13¼ hours. $40.

October 29-31—**Southern California Psychiatric Society Annual Convention.** Santa Barbara Biltmore Hotel. Friday-Sunday. Contact: Ralph M. Obler, M.D., 11860 Wilshire Blvd., Los Angeles 90025.

NOVEMBER

November 3-4—**A Practical Approach to the Diagnosis and Treatment of Arrhythmias and Conduction Defects.** USC at Ambassador Hotel, 3400 Wilshire, Los Angeles. Wednesday-Thursday. 16 hours. $50.

November 5-6—**California Hospital Seminar on the Acute Abdomen.** California Hospital, 1414 South Hope Street, Los Angeles. Friday-Saturday. 12 hours. Contact: Kenneth L. Senter, M.D., Director of Medical Education, California Hospital.

November 5-6—**The Compensable Injury.** USC at Orthopedic Hospital, 2400 South Flower Street, Los Angeles. Friday-Saturday. 12 hours. $60.

November 5-6—**Comprehensive Medical Care and the Psychiatric Consultation.** UCSF. Friday-Saturday. 9 hours. $20.

November 5-6—**Diseases of the Biliary System.** UCSF. Friday-Saturday. 10¾ hours. $40.

November 6—**The Electrocardiogram in Coronary Artery Disease.** Stan. Saturday. 8 hours. $20.

November 6-7—**The Somatic Mask of Psychiatric Illness.** UCSF at Fresno Community Hospital, Fresno. Saturday-Sunday. 10⅓ hours. $10.

November 10—**The Southern California Annual Science Lecture of The American College of Physicians.** Statler Hilton Hotel, Los Angeles. Wednesday, 6:30 p.m. Contact: W. Philip Corr, M.D., Governor for Southern California, The American College of Physicians, 3660 Arlington Avenue, Riverside 92506.

November 11-13—**Gerontological Society.** Ambassador Hotel, Los Angeles. Thursday-Saturday. Contact: Mrs. Marjorie Adler, Gerontological Society, 661 S. Euclid, St. Louis 63110.

November 11-13—**Annual Western Institute on Epilepsy.** Kona Kai Club, Shelter Island, San Diego. Thursday-Saturday. $10. Contact: Manuel Barba, M.D., San Diego County Epilepsy Society, 1612 30th Street, San Diego 92102.

November 12-13—**Central Nervous System Infections.** UCSF. Friday-Saturday. 12 hours. $40.

November 12-13—**Hyperbaric Oxygen and Radiation Therapy of Cancer.** Saroni Memorial Tumor Institute of San Francisco, 1600 Divisadero Street. Friday-Saturday. 12 hours. Contact: Jerome M. Vaeth, M.D., director, Saroni Memorial Tumor Institute of San Francisco.

November 12-13—**Kaiser Foundation Hospitals Symposium on Genetics.** Statler Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Herman Weiner, M.D., Permanente Medical Group, 1505 North Edgemont, Los Angeles 90027.

November 13-14—**First Annual Clinical Cancer Conference.** UCSF in cooperation with California Division, American Cancer Society. Friday-Saturday. 13¼ hours. $20.

November 14—**Current Cancer Chemotherapy.** UCLA at Glendale Sanitarium—Annual Meeting. Sunday.

November 16-17—**Albert M. Snell Memorial Lectures.** Presented by the Palo Alto Medical Research Foundation. Palo Alto Medical Clinic Auditorium. Tuesday and Wednesday evenings at 8:00 p.m. Contact: Edward E. Daleske, assistant director, Palo Alto Medical Research Foundation, 860 Bryant St., Palo Alto.

November 17—**Santa Barbara Cottage and General Hospitals Program on Advances in Medical Practice.** Santa Barbara Cottage Hospital. Wednesday. 3 hours. Contact: C. A. Domz, M.D., 317 West Pueblo, Santa Barbara.

November 17-February 9—**Psychiatric Case Conferences-Section 2.** USC at Memorial Hospital of Long Beach. Wednesday evenings. 24 hours. $35.

November 19-20—**Fear and Pain Control: A Practical Approach.** UCSF. Friday-Saturday. $40.

November 23-February 15—**Psychiatric Case Conferences-Section 4.** USC at Valley Presbyterian Hospital, Van Nuys. Tuesday evenings. 24 hours. $35.

November 30-February 22—**Psychiatric Case Conferences-Section 5.** USC at Hawthorne Community Hospital. Tuesday evenings. 24 hours. $35.

DECEMBER

December 1—**St. Luke Hospital Annual Postgraduate Assembly.** St. Luke Hospital Staff Room, Pasadena. Wednesday. 8 hours. Contact: R. D. Miller, M.D., chairman, Annual Postgraduate Assembly, 615 East Union Street, Pasadena 91101.

December 1-4—**Ophthalmology Symposium: Retinopathy and Diabetes.** UCSF. Wednesday-Saturday.

December 1-March 2—**Psychiatric Case Conferences-Section 1.** USC. Wednesday evenings. 24 hours. $35.

December 1-March 2—**Psychiatric Case Conferences-Section 3.** USC at Santa Monica Hospital. Wednesday evenings. 24 hours. $35.

December 2-3—**Medicine Megalopolis.** USC at Ambassador Hotel, 3400 Wilshire Blvd., Los Angeles. Thursday-Friday. 16 hours. $25.

December 2-4—**California Society of Pathologists—Data Processing in Laboratory Medicine.** Disneyland Hotel, Anaheim. Thursday-Saturday. Contact: Weldon K. Bullock, M.D., 1200 N. State Street, Los Angeles.

December 2-4—**Microangiopathy of the Eye in Diabetes.** UCSF. Thursday-Saturday. 16½ hours. $75.

December 3-4—**Vectorcardiography.** UCSF. Friday-Saturday. 11½ hours. $40.

December 3-5—**Fluid and Electrolyte Balance.** USC at the Riviera Hotel, Palm Springs. Friday-Sunday. 15 hours. $60.

December 7-March 1—**Psychiatric Interviewing in Medical Practice.** USC. Tuesday evenings. 24 hours. $35.

December 8—**Tuberculosis and Health Association of Alameda County Annual Symposium-Seminars on Respiratory Diseases.** Co-sponsored by the Alameda-Contra Costa Academy of General Practice. Berkeley House Hotel/Motel, Berkeley. Wednesday. 6 hours. Contact: E. Ronald Riggall, M.D., chairman, 121 E. 11th Street, Oakland.

December 11—**Medical Emergencies.** Pres. Med. Ctr. Saturday. 8 hours. $30.

December 11-12—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton, Saturday-Sunday. 12 hours. $10.

JANUARY

January 8—**Human Development and Birth Defects.** UCSF at Childrens Hospital, San Francisco. Saturday. 5½ hours. $15.

January 15—**Conference on Neurologic Evaluation.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 18-April 12—**Medical Radio Conferences.** UCSF. Tuesdays, 12:30-1:30 p.m.

January 19—**Los Angeles County Heart Association Annual Midwinter Symposium.** Statler Hilton Hotel, Los Angeles. Wednesday. 6 hours. Contact: Harold Miller, M.D., chairman, Professional Education Committee, 2405 W. Eighth Street, Los Angeles 90057.

January 19—**Riverside County General Hospital Postgraduate Assembly.** Riverside County General Hospital. Wednesday. 12 hours. Contact: Harold A. Roth, M.D., Riverside County General Hospital, 9851 Magnolia Avenue, Riverside 92503.

January 19-April 20—**Psychotherapeutic Principles and Practice for Non-Psychiatrists.** UCSF. Wednesdays. 70 hours. $25.

January 19-May 18—**Teaching Clinics in Psychiatry.** UCLA. Wednesdays.

January 20-21—**New and Old Antibiotics.** USC. Thursday-Friday.

January 20-April 7—**Medical Radio Conferences.** UCSF. Thursdays, 12:30-1:30 p.m.

January 21-23—**A Time for Decision: The Biologic Crossroad.** UCSF. Friday-Sunday.

January 22—**Pediatric Cardiology Symposium.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 28—**Nuclear Medicine.** USC. Friday.

January 28-30—**Clinical Conference in Pediatric Anesthesiology.** Friday-Sunday. Contact: M. Digby Leigh, M.D., Childrens Hospital of Los Angeles, 4614 Sunset Blvd., Los Angeles 90027.

January 29—**Practical Proctology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 31-February 1—**Uroradiology.** UCLA. Monday-Tuesday.

FEBRUARY

Februrary 1-March 22—**Isotope Techniques in the Health Sciences.** UCSF. Tuesdays.

February 1-April 19—**Bedside Cardiology.** USC at Los Angeles County Hospital. Tuesdays.

February 2-4—**Aviation Medicine Seminars.** UCSF at Del Webb's Townehouse, San Francisco. Wednesday-Friday.

February 3-4—**SOUTHERN COUNTIES—Regional Postgraduate Institute presented by California Medical Association** in cooperation with USC School of Medicine. El Mirador Hotel, Palm Springs. "Hematology and Infectious Diseases and Antibiotics." Chairman: Robert M. Zweig, M.D., 3875 Jackson, Arlington.

February 4-5—**New Potentials in the Treatment of Common Diseases.** UCSF. Friday-Saturday.

February 4-March 11—**Psychiatry in Daily Practice.** UCSF at Mercy Hospital, Redding. Fridays.

February 7—**Medical Aspects of Well Being: Emotional Aspects of Rehabilitation.** UCSF. Monday.

February 9—**Symposium on Shock.** USC. Wednesday.

February 10-11—**Symposium on Endocrinology.** USC. Thursday-Friday.

February 10-12—**Pediatric Ophthalmology.** UCSF. Thursday-Saturday.

February 11-13—**American College of Physicians, Northern California and Nevada Regional Meeting.** Mark Thomas Inn, Monterey. Friday-Sunday. 10 hours. Contact: Roberto F. Escamilla, M.D., Governor, Northern California and Nevada Region, American College of Physicians, 897 Hyde Street, San Francisco.

February 12—**Surgical Emergencies.** Pres. Med. Ctr. Saturday. 8 hours. $30.

February 12-13—**Cystic Fibrosis.** UCLA. Saturday-Sunday.

February 12-13—**A Symposium on Hypnosis.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

February 12-13—**Law-Science-Medicine.** UCSF. Saturday-Sunday.

February 14-16—**Institute for Metabolic Research Dynamics of Endocrine and Metabolic Disease Annual Symposium.** Highland Hospital. $30. Contact: L. W. Kinsell, M.D., director, Institute of Metabolic Research, 2701 14th Ave., Oakland.

February 14-18—**American College of Chest Physicians —Clinical Application of Cardio-Pulmonary Physiology.** Ambassador Hotel, Los Angeles. Monday-Friday. Contact: Alfred Goldman, M.D., program chairman, Suite 906, 9201 Sunset Blvd., Ios Angeles 90069.

February 14-18—**Course for Physicians in General Practice.** UCSF at Mt. Zion Hospital, San Francisco. Monday-Friday.

February 16-20—**Controversial Areas in Surgery.** UCLA at Palm Springs. Wednesday-Sunday.

February 18-19—**Pediatric Dermatology.** UCSF. Friday-Saturday.

February 18-20—**American College of Physicians Southern California Regional Meeting.** Biltmore Hotel, Santa Barbara. Friday-Sunday. Contact: W. Philip Corr, M.D., governor, 3660 Arlington Ave., Riverside 92506.

February 19-20—**Neuropsychiatry in Daily Practice.** UCSF in Salinas and Monterey. Saturday-Sunday.

February 20-23—**Current Concepts in Chemotherapy.** UCLA at Palm Springs. Sunday-Wednesday.

February 24-25—**Medical-Surgical Gastroenterology Conference.** USC. Thursday-Friday.

February 25-26—**Workshop on Hand Injuries.** Pres. Med. Ctr. Friday-Saturday. 12 hours. $75.

February 25-27—**Conference on Mental Retardation for Physicians.** UCSF. Friday-Sunday.

February 27-March 2—**Surgical Applied Anatomy.** LLU. Sunday-Wednesday. 29½ hours.

MARCH

March 2-3—**Los Angeles County Heart Association Annual Spring Symposium.** Statler Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hours. Contact: Harold Miller, M.D., chairman, Professional Education Committee, 2405 W. Eighth Street, Los Angeles 90057.

March 3-4—**Symposium on Diabetes.** USC. Thursday-Friday.

March 4-5—**Gynecological Problems for the Non-Gynecologist.** UCSF. Friday-Saturday.

March 4-5—**Operable Heart Disease.** Pres. Med. Ctr. Friday-Saturday. 16 hours. $35.

March 5-6—**The Knee.** UCLA. Saturday-Sunday.

March 5-6—**Sexual Conflicts and Adjustments.** UCSF at Herrick Hospital, Berkeley. Saturday-Sunday.

March 9-11—**Conference on Keratoplasty.** Pres. Med. Ctr. Wednesday-Friday. 21 hours. $125. Contact: Jerome W. Bettman, M.D., 2400 Clay St., San Francisco.

March 9-13—**Diagnostic Radiology.** UCSF. Wednesday-Sunday.

March 10-14—**Pulmonary Problems.** UCLA. Thursday-Sunday.

March 11-12—**Childrens Hospital Medical Center Annual Postgraduate Seminar and Clifford D. Sweet Lecture.** Childrens Hospital, 51st and Grove Streets, Oakland. 8 hours. $30 for 4 sessions or $10 per session. Contact: Childrens Hospital Medical Center, Oakland.

March 11-12—**WEST COAST COUNTIES—Regional Postgraduate Institute presented by California Medical Association** in cooperation with UCSF. Ojai Valley Inn, Ojai. "Indications for Surgical Intervention—The Difficult Decision." Chairman: George J. Wittenstein, M.D., 2235 Castillo, Santa Barbara.

March 12—**Cancer: Childhood and Adult Tumors.** UCSF at Childrens Hospital, San Francisco. Saturday.

March 12—**Obstetrics and Gynecology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

March 12-13—**Neuropsychiatry in Daily Practice.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

March 13-17—**Alumni Postgraduate Convention,** LLU. Mar. 13-14 (Sunday-Monday)—Refresher Courses. White Memorial Medical Center. Mar. 15-17 (Tuesday-Thursday)—Scientific Assembly. Ambassador Hotel, Los Angeles. Contact: Samuel H. Fritz, M.D., general chairman, 1832 E. Michigan Avenue, Los Angeles 90033.

March 16—**Annual Postgraduate Symposium on Heart Disease.** O'Connor Hospital, San Jose. Wednesday. $15., incl. lunch. Contact: William G. Allayaud, executive director, Santa Clara County Heart Association, 1961 The Alameda, San Jose 95126.

March 16—**Symposium on Obesity.** USC. Wednesday.

March 19—**Rheumatic Diseases.** Pres. Med. Ctr. Saturday. 8 hours. $30.

March 19-20—**California Radiological Society Annual Meeting.** Biltmore Hotel, Los Angeles. Saturday-Sunday. Contact: L. H. Garland, M.D., 450 Sutter Street, San Francisco.

March 20-23—**CALIFORNIA MEDICAL ASSOCIATION 94th Annual Session.** Scientific theme: "CURRENT CONCEPTS IN THERAPY: Coronary Artery Disease. Gastrointestinal Hemorrhage. Renal Failure." Biltmore Hotel, Los Angeles. Sunday-Wednesday. Contact: Mr. John Hunton, executive secretary, 693 Sutter Street, San Francisco 94102.

March 25-27—**Postgraduate Assembly in Anesthesiology.** Sponsored by the Anesthesia Section, Los Angeles County Medical Association. International Hotel, Los Angeles. Friday-Sunday. $25. Contact: Thomas W. McIntosh, M.D., secretary, Postgraduate Committee, 686 East Union Street, Pasadena.

March 25-27—**Sex Disorders in Clinical Practice.** UCSF. Friday-Sunday.

March 26—**Endocrinology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

APRIL

April 1-2—**Contrast Media in Abdominal Disease: A Program for the Practicing Physician.** UCSF. Friday-Saturday.

April 1-2—**Joint Manipulations in Perspective.** UCSF. Friday-Saturday.

April 4-8—**Mental Retardation Institute.** USC. Monday-Friday.

April 6-27—**Advanced Funduscopy.** USC. Wednesdays.

April 6-May 11—**Psychiatry in General Practice.** UCSF at Stockton State Hospital, Stockton. Wednesdays.

April 7-June 9—**Ward Walks in Rare Diseases.** USC. Thursdays.

April 12-June 14—**Bedside Cardiology.** USC at St. Vincent's Hospital. Tuesdays.

April 16—**Sports Injuries.** UCLA. Saturday.

April 16-17—**The Uncertain Quest: The Teen-Ager's World.** UCSF. Saturday-Sunday.

April 21-23—**Endocrinology and Metabolism.** UCSF. Thursday-Saturday.

April 23-24—**Neuropsychiatry for the Non-Psychiatric Physician in General Practice.** UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday.

April 25-27—**Annual Meeting of the Council on Medical Television.** UCSF. Monday-Wednesday. Contact: Irving Merrill, M.D., director, Office of Television Research, UCSF.

April 28-29—**General Surgery.** UCSF. Thursday-Friday.

April 28-29—**Symposium on Hypertension.** USC. Thursday-Friday.

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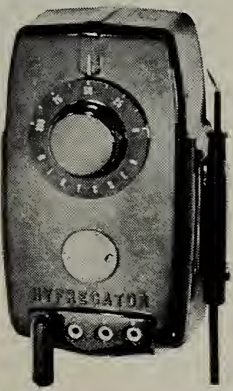

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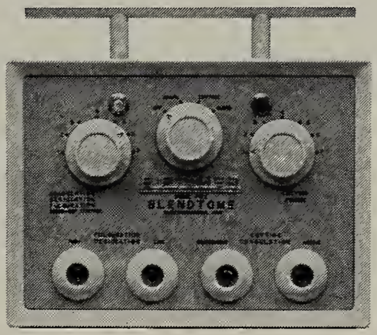

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March 1966 Date Set for Annual Sight-Saving Conference

The 1966 annual Sight-Saving Conference of the National Society for the Prevention of Blindness, Inc. will be held at the Hotel Roosevelt, New York, N.Y., from March 30 through April 1, 1966. The program and speakers for the three-day national gathering will be announced later this year by the National Society.

No Side Effects Found For Tampons

The use of tampons in menstrual hygiene has no undesired physiological or clinical side effects, according to an article in the May 24 *Journal of the American Medical Association.*

A study of 903 women, about half of whom used tampons, "failed to reveal any condition which appears to be adversely influenced by tampons," the report said.

This was found to be true even when tampons were used in the presence of injury or inflammation, the report said. It was pointed out, however, that there were no cases of genital tract cancer among the women studied, and that no correlation could be made between this disease and the type of menstrual hygiene chosen.

"Nevertheless, we have no reason to regard the type of menstrual hygiene as a factor in malignancy of the genital tract," the investigators said.

The report is by Robert E. Wheatley, M.D., Miriam F. Menkin, M.A., Eleanor Dooks Bardes, R.N., and John Rock, M.D., all of the Rock Reproductive Clinic, Inc., Brookline, Mass.

"The insertion of cottonlike material in the vagina is not an innovation," the report said. "Fifteen centuries before Christ there was reference to the use of medicated lint tampons in the vagina for contraception.

"However, although physicians had employed tampons therapeutically for more than a century, it was not until 1936 that a commercial, patented product for the intravaginal absorption of menstrual fluid became popular," the report said.

"The public acceptance of (tampons) seems to have stimulated those who tend to stigmatize as malicious that which is new. Thus, for some years after their introduction, tampons were implicated in a spectrum of diseases and conditions, ranging from endometriosis, cervicitis, and vaginitis to defloration, immorality, and contraception," the report said.

However, based on their study and review of the medical literature, the investigators said "it would appear that tampons have no deleterious effects, physiologically, clinically, or morally."

The study of the 903 women was based on approximately 2,627 patient-years of experience with tampons and an estimated 9,524 patient-

(Continued on Page 50)

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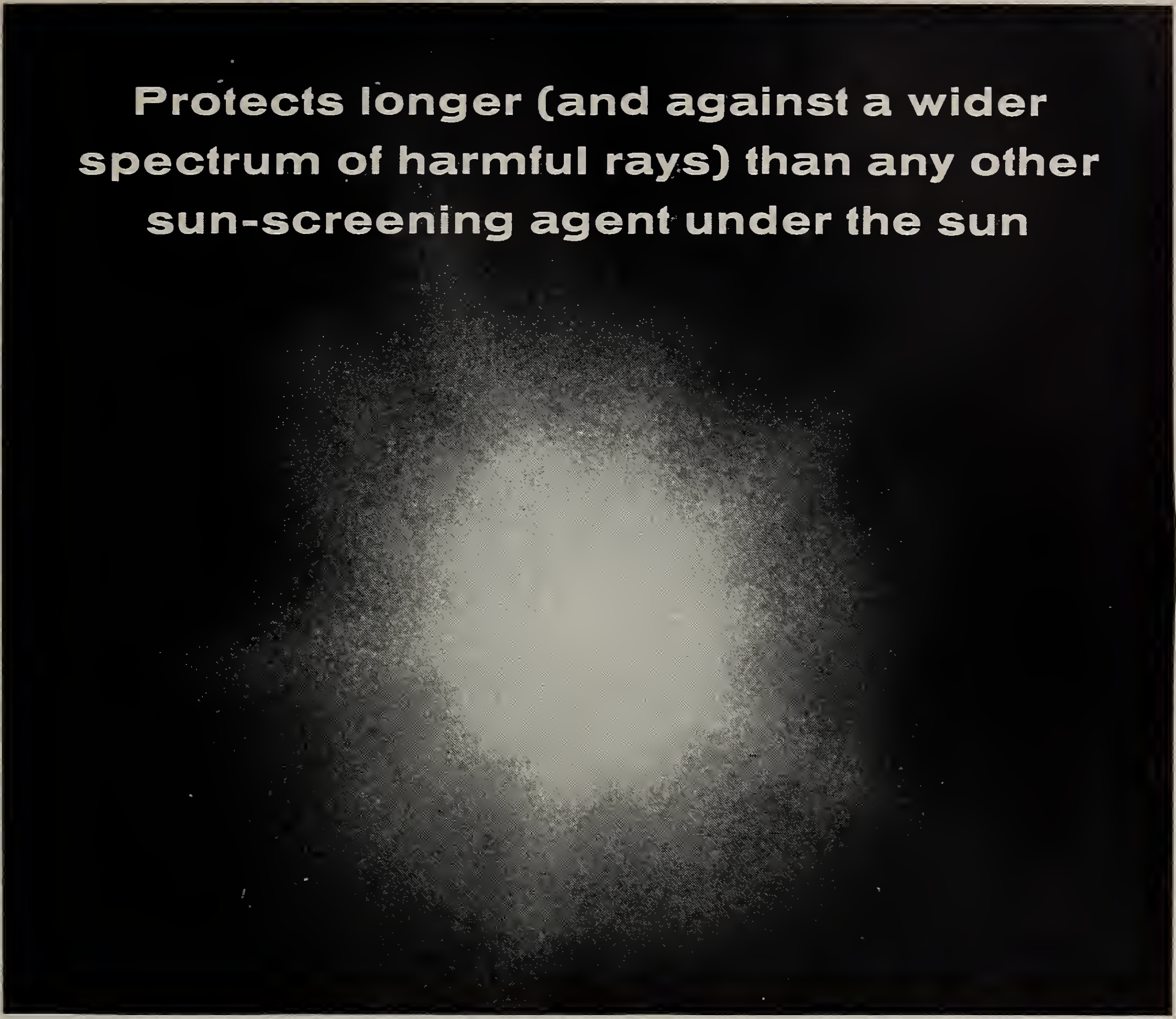
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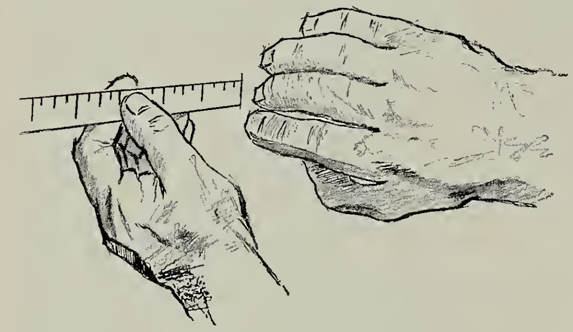

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No Side Effects Found For Tampons

(Continued from Page 46)

years among those who used external pads alone. Some patients alternated types of hygienic protection during the menstrual period.

TB Still Serious Disease

Tuberculosis-caused deaths have declined dramatically in the U.S. during the past 60 years, but there are over 9,000 deaths and 50,000 new cases of TB in the country each year, and increasing rates have been reported in some cities.

Nonwhite TB death rates remain 2½ to 3½ times higher than those of whites, and three times as many males as females die from tuberculosis, according to a report in the June 21 *Journal of the American Medical Association.*

The report is by Theodore C. Doege, M.D., of the department of preventive medicine, University of Washington School of Medicine, Seattle.

"These facts . . . remind us that tuberculosis remains a significant health hazard. About 75 per cent of new cases occur among the estimated 35 million tuberculin-positive individuals, with persons among lower socioeconomic groups and in metropolitan areas, the elderly, and the chronically ill being at special risk," said a JAMA editorial.

Measures which will help break the chain of tuberculosis infection, said the editorial, include tuberculin tests and chest x-rays of case contacts, establishment of case registries, chemotherapy and long-term follow-up of cases, BGG vaccination, and use of the chemical isoniazid in treating TB.

From 1900 to 1960, tuberculosis death rates in the U.S. fell from 194.1 to 6.1 deaths per 100,000.

Decreases in the death rate began in the latter part of the 19th century, Dr. Doege said, and preceded by more than 50 years the introduction of antituberculous chemotherapy and antibiotics.

"Thus, the history of tuberculosis mortality underscores the concept that dramatic decreases in death rates from an infectious disease may be related to environmental changes in working conditions, nutrition, sanitation, and housing, as well as to dramatic medical advances," the report said.

"It is a safe assumption that social and economic influences are also of great importance in the consistently higher tuberculosis rates among nonwhites," Dr. Doege said.

Men have higher TB death rates than women, except in the 5-to-25-year age group. The higher female rate in this group may be due to factors associated with stress, childbearing and childrearing, the report said.

Reasons for the otherwise higher mortality rates in males are not clear, the report said. Possible reasons are improvements in women's home and working conditions, their generally better record of following medical advice, and the greater prevalence of chronic disease in men, the report said.

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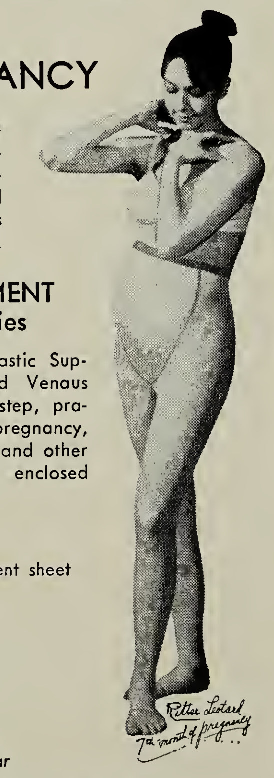

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BOOKS RECEIVED

(Continued from Page 16)

and Attending Physician, Evanston Hospital Association, Evanston, Illinois; and Alvah L. Newcomb, M.D., Associate Professor of Pediatrics, Northwestern University Medical School; Associate Attending Physician, Children's Memorial Hospital, Chicago, Illinois; and Attending Physician, Evanston Hospital Association, Evanston, Illinois. The C. V. Mosby Company, St. Louis, 1965. 147 pages, $12.75.

MEDICAL DEPARTMENT, UNITED STATES ARMY, SURGERY IN WORLD WAR II—Thoracic Surgery, Volume II—Prepared and published under the direction of Lieutenant General Leonard D. Heaton, The Surgeon General, United States Army. Colonel Arnold Lorentz Ahnfeldt, MC, USA, Editor in Chief; Frank B. Berry, M.D., Editor for Thoracic Surgery; Elizabeth M. McFetridge, M.A., Associate Editor. Office of The Surgeon General, Department of the Army, Washington, D.C., 1965. 615 pages, available for purchase at $7.25 per copy from the Superintendent of Documents, Government Printing Office, Washington, D.C., 20402.

MEDICINE IN TRANSITION—Iago Galdston, M.D. The University of Chicago Press, Chicago, Ill., 1965. 220 pages, $5.95.

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Lincoln Autopsy Report Reviewed

Controversy continues about the details of the autopsy on Abraham Lincoln.

In the August 2 *Journal of the American Medical Association,* a recently discovered autopsy report by Lincoln's personal physician is reviewed by John K. Lattimer, M.D., of Columbia University, New York.

It had been hoped that the report by Dr. Robert King Stone would resolve the question of Lincoln's fatal wound. Some observers at the time swore the bullet fired by John Wilkes Booth entered on the left side of the head; others said it was on the right side.

Dr. Lattimer's conclusion, after reviewing Dr. Stone's handwritten report and a diagram: the details of the wound still aren't clear.

Dr. Stone's notes clearly state that the bullet "lodged in cerebral matter . . . on the left side." His diagram, however, doesn't make this clear.

Other doctors at the time just as emphatically stated that the President's wound was on the right side of his head.

How could medical authorities disagree on such a fundamental point? Doctor Lattimer supplies an answer:

"It must be remembered that all of the doctors who made these statements had been awake continuously for at least 30 hours, under the most severe emotional stress, by the time they attended the autopsy. There was great confusion as to how the bullet hole came to be in the left side of Mr. Lincoln's head, since Booth had approached him from his (Lincoln's) right side. Against this background there is little wonder that conflicting testimony appeared."

Dr. Stone's handwritten autopsy report is in the custody of the New York State Historical Association, Cooperstown, N.Y.

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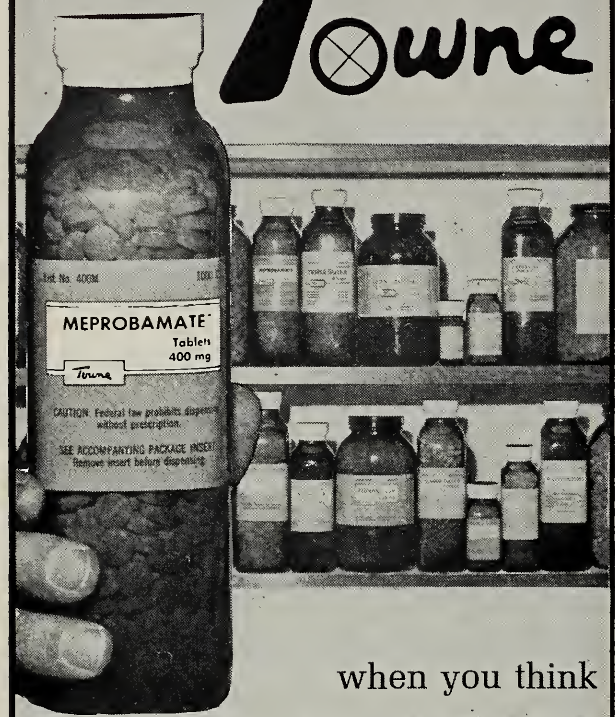

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Voluntary Health Conference Scheduled

Changing relationships in the voluntary health movement will be the theme of a national invitational conference here Feb. 16-17, 1966, sponsored by the American Medical Association Council on Voluntary Health Agencies.

The conference will consider the influence of present and future voluntary and public forces on health agencies.

Subjects to be considered include communications and public attitudes, community planning, expenditures, legal patterns, continuing professional education, and relationships between government and volunteerism.

Those invited include more than 300 representatives of the medical profession, national organizations, voluntary health and welfare agencies, business, labor, government, and education.

The conference will convene with a major address entitled, "Horizons in Communications and their Application to Public Attitudes," following a reception and dinner Wednesday evening, Feb. 16. Four general sessions and two major addresses will follow on Thursday, Feb. 17. The conference will adjourn at 4:30 p.m. that day. Registration will begin at 4 p.m. Wednesday, Feb. 16, at the Continental Plaza Hotel.

Recovering from "Heart Attacks"

Frightened and depressed after suffering an acute "heart attack," a patient sometimes is convinced he is sicker than he really is.

The result may be lingering invalidism which works a hardship on both the patient and his family, points out an article in the October 11 *Journal of the American Medical Association.*

Staff members at Duke University School of Medicine examined 20 men who were making slow progress in recuperating from acute myocardial infarction (coronary artery obstruction). They found:

1. Widespread belief among patients and their families that the heart remains "very fragile" after an attack. There was great fear of physical activity.
2. Depression and frequent chest pains in the men, although these pains were not related to the attack.
3. Overprotectiveness by some patients' wives. Even when some men made an effort to return to normal activities, their wives wouldn't let them. On the other hand, some men were overcautious themselves.

The authors of the article are Robert F. Klein, M.D., Alfred Dean, Ph.D., L. Montgomery Willson, and Morton D. Bogdonoff, M.D.

The sample of 20 patients cannot be considered representative of all cases of myocardial infarction, the authors point out, but these patients represent characteristics that many physicians have observed.

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New Volume on Cutaneous Toxicity

"Cutaneous Toxicity," symposium by American Medical Association and Society of Toxicology, October 1965, Clothbound, $8; paperbound, $6.

The effects of new chemicals on the human skin is the subject of a new volume to be published by the American Medical Association in cooperation with the Society of Toxicology.

"Cutaneous Toxicity" contains papers presented at a recent symposium sponsored by the two groups, and concerned with problems resulting from chemical contact with human skin.

Contributors to the symposium are experts from many scientific disciplines. Much of the information they presented has not been generally available until publication of this volume. The foreword is by Harry W. Hays of the Advisory Center on Toxicology, the National Academy of Sciences, and National Research Council.

The book will be of special value to those interested in the physiology of the skin and cutaneous health. Topics include the nature of the epidermal barrier, the adequacy of existing skin treatment techniques, and the problem of relating animal research data to man.

The volume will appear in October as a supplement to Toxicology and Applied Pharmacology, official journal of the Society of Toxicology.

Copies are available at $6, paperbound, or $8, clothbound, from Academic Press Inc., 111 Fifth Avenue, New York, New York 10003.

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AMA Extends Its Campaign Against V.D.

As part of its nationwide campaign against venereal disease, the American Medical Association last week sent educational announcements to more than 2,500 radio stations and 300 television stations.

At the end of October, 50,000 two-color posters and 300,000 pamphlets outlining the dangers of V.D. were sent to schools, state and local medical societies, and other health agencies.

The one-minute, animated TV spot announcements tell listeners that venereal disease is spreading in a wave of infection, and that early and continued medical treatment can cure V.D.

Sixty-second and 20-second radio announcements outline much the same message, pointing out that if left untreated, V.D. can blind, cripple, or even kill. Wide use has been made of the announcements. Several stations have supported the campaign with broadcast editorials.

The AMA opened its educational campaign last month, saying that V.D. now has become this nation's "most urgent communicable disease problem."

The two most serious veneral diseases, syphilis and gonorrhea, are infecting 1,100,000 Americans a year—about 2,300 a day, or almost two a minute. Cases of infectious syphilis have almost trebled in this country in the past five years.

Complacency, ignorance, a free-and-easy attitude toward moral standards, increasing use of alcohol and homosexuality are some of the reasons for the increase in venereal disease. Many young people simply aren't aware of the dangers of V.D.

Syphilis and gonorrhea can be easily cured. The cure for both diseases—penicillin—has been available since 1943. If a person suspects he may have contracted venereal disease, he should go to his physician immediately.

California
Medicine

Chemical Approaches to Selective Inhibition of Viral Multiplication

IGOR TAMM., M.D., AND HANS J. EGGERS, M.D., *New York*

■ *There are more than 300 immunological types of viruses that infect man, but most are members of only eight major groups, each group characterized by distinguishing physical and chemical features. Chemical inhibitors have been discovered which are selectively directed against members of individual groups of viruses. These inhibitors interfere with virus-specific processes and have no effects on host cell metabolism at concentrations sufficient to prevent or stop virus multiplication. The biochemical basis of such selective action is understood in some cases. In addition, synthetic chemicals and biological products are known that inhibit members of several groups of viruses. The basis of their selective action is not clear.*

A VIRUS PARTICLE may be considered to be a small packet of genetic material. In virus infection, the protein coat of the virus particle reacts with specific receptor molecules on the surface of a susceptible cell. The virus particle attaches and is taken into the cell in a phagocytic vesicle. The viral genetic material, ribonucleic acid (RNA) or deoxyribonucleic acid (DNA), is then freed of its protective protein coat and proceeds to direct the synthesis of virus-specific proteins and nucleic acid in the infected cell. New virus particles are assembled from newly synthesized viral nucleic acid and proteins, except that in some virus-cell systems complete virus is not produced. The infection spreads to other susceptible cells as new virus is released or directly transmitted to neighboring cells or to daughter cells.

In theory, specific inhibition of viral multiplication can be accomplished at each of several steps in the process of viral reproduction, as viral proteins and virus nucleic acid are macromolecules endowed with a high degree of specificity and possess specialized functions. The small-molecular building blocks out of which viral macromolecules are made are common to virus and host cells. The specificity of the macromolecular components of viruses and of virus-directed enzyme proteins resides primarily in the sequence of the building blocks—that is, the nucleotides and amino acids—and finds expression in the three-dimensional configuration of the viral macromolecules.

Targets for Selective Inhibitors

We may postulate that a virus-specific inhibitor would be one that recognizes and combines with a particular site on a viral or virus-directed macromolecule. Such an inhibitor might combine with a reactive site on the viral protein coat and thereby block an early step in infection, such as attachment of the virus to or penetration into cells. Alternatively, an inhibitor might form a complex with the viral nucleic acid that has entered the

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From the Rockefeller University, New York.

Aided by a grant from The National Foundation.

Presented before the Second General Meeting at the 94th Annual Session of the California Medical Association, San Francisco, March 28 to 31, 1965.

cell, and prevent its functioning by blocking the transcription or translation of the viral genetic information. Another possibility is that an inhibitor might block a step in the biosynthetic pathway of viral protein synthesis. Finally an inhibitor might interfere with the enzymatic or the structural function of a virus-directed protein.

Thus, according to current concepts there are several ways of inhibiting specifically the replication of a virus. The old view that there was no way of inhibiting a virus without at the same time inhibiting the cell overlooked the chemical and biological specificity of viral macromolecules. The outstanding problem in selective inhibition is that of finding compounds which can recognize virus-specific features of viral macromolecules. The exact chemical basis of the specificity of the viral nucleic acid and proteins of different viruses is not yet known. It has therefore not been possible to consider, on a precise theoretical basis, the structural requirements for specific inhibitors for different viruses. The definition of the three-dimensional structures of biologically important macromolecules is one of the most exciting fields in modern biology, and the delineation of the active sites on biological macromolecules is one of the outstanding challenges in the field. As knowledge of virus-specific features of viral macromolecules increases, it may prove possible to design inhibitors which will specifically and predictably combine with virus-specific targets.

Meanwhile, through educated guesses and empirical approaches, a number of selective inhibitors of viral reproduction have become available in recent years. With some of the inhibitors the first successes in the chemoprophylaxis and chemotherapy of viral infections have been recorded.

Major Groups of Animal Viruses

One important recent development in virology has been the recognition that the hundreds of immunological types of viruses known to exist fall into relatively few major groups, characterized by common physical and chemical features.[21] There are four major groups of DNA-containing viruses, which according to size may be arranged as follows: poxviruses, herpesviruses, adenoviruses, and papovaviruses (papilloma and related agents). Viruses in two of the DNA-virus groups possess an outer lipid-containing envelope (pox and herpes); viruses in the other two do not (adeno and papova).

The four RNA-virus groups are myxoviruses (including influenza and mumps viruses), reoviruses (unique among RNA viruses as they possess double-stranded RNA), arthropod-borne viruses (many arboviruses cause encephalitis) and picornaviruses (polioviruses, Coxsackieviruses, echoviruses and rhinoviruses). As with the DNA-viruses, two of the RNA-virus groups are characterized by the presence of a lipid-containing envelope around the viral nucleocapsid (myxo and arbo), whereas viruses in two other groups lack such an envelope (reo and picorna). Subgroups have been delineated within some of the major groups. Some viruses have not yet lent themselves to grouping.

It would be reasonable to expect that viruses which belong to a particular group possess common group-specific biochemical features. If this be so, a single inhibitor might inhibit many or all members of one major group of viruses but have no significant effects on representatives of other major groups of viruses. It has been shown that certain chemical inhibitors behave exactly in this way in that they are group-specific, or even subgroup-specific. Selective inhibitors have been found for the smallest and simplest viruses: hydroxybenzyl-benzimidazole and guanidine inhibit many picornaviruses.[34] Selective inhibitors have also been found for the largest and most complex viruses: Isatin β-thiosemicarbazone and its derivatives inhibit poxviruses.[3,32] Recently it has been discovered that 1-adamantanamine inhibits certain myxoviruses.[9]

However, it has already become clear that there are also inhibitors that inhibit members of more than one group of viruses. 5-Iodo-2′-deoxyuridine (IUDR) inhibits many DNA-viruses,[23] but its selective action seems to be restricted to sites such as the eye where topical application is possible.[25,26] In such sites the conditions for therapeutic effects are particularly favorable.

None of the selective inhibitors that will be discussed has a direct irreversible inactivating effect on the virus particle. The inhibitors do not destroy virus particles, but instead block virus functions. At the concentrations which are sufficient to inhibit the multiplication of sensitive viruses, the group-specific inhibitors do not interfere with such fundamental cellular processes as energy metabolism, cellular nucleic acid or protein synthesis, or cell division.

1-Adamantanamine

1-Adamantanamine is a symmetric tricyclic primary amine. This compound inhibits the multiplication of several influenza viruses both in cell culture and in the mouse.[9] Parainfluenza, mumps, and measles viruses do not appear to be sensitive. It has been reported that 1-adamantanamine does not interfere with the adsorption of influenza virus to cells, but may interfere with some other early step in infection, such as penetration of host cells by virus. When the virus-inhibitory effects of 1-adamantanamine were first reported in the spring of 1964 the findings were received with considerable interest as they provided a new approach to selective inhibition of myxoviruses. The practical aspects, such as effectiveness and side effects in man, of the possible use of 1-adamantanamine in the prevention of influenza are under investigation in several laboratories.

Hydroxybenzyl-benzimidazole and Guanidine

2-(α-Hydroxybenzyl)-benzimidazole (HBB) and guanidine • HCl inhibit the multiplication of many small RNA viruses such as poliovirus.[34] HBB is an aromatic and heterocyclic carbanol, whereas guanidine is an imino derivative of urea. Because the action of HBB and guanidine is highly specific, they are useful reagents in the laboratory diagnosis and differentiation of picornaviruses.[13,14,33]

Detailed studies of the mechanism of action have shown that these compounds have no effect on the adsorption or penetration of virus. HBB and guanidine do not block infection of susceptible cells, but they specifically inhibit the synthesis of viral RNA polymerase, the virus-directed enzyme which is responsible for viral RNA synthesis.[2] The action of HBB and guanidine on picornavirus multiplication establishes that where a virus makes its own nucleic acid polymerase, it is possible to inhibit the synthesis of such a virus-specific protein by means of small-molecular compounds which have no effect on cellular biosynthesis. When the synthesis of viral RNA polymerase is inhibited, viral RNA cannot be made.[12,15,17] Furthermore, as the viral RNA functions as messenger RNA in the synthesis of viral coat proteins, little or no coat proteins are made in the treated cells.[8,15]

HBB and guanidine are valuable tools in the study of the biochemical genetics in animal viruses. When virus-infected cultures are incubated with HBB or guanidine, viral mutants emerge which may be either drug-resistant or drug-requiring.* The drug-resistant virus is able to make viral RNA polymerase *even* when the drug is present, whereas the dependent virus can make the enzyme *only* when the drug is present.[2]

HBB and guanidine show only partial cross resistance—that is, when a mutant is obtained that is decidedly resistant to one drug, it may not be equally resistant to the other, and vice versa.[33] It is also of considerable interest that HBB and guanidine act synergistically.[19] These findings provide an adequate explanation for the fact that combined treatment of infected cells with HBB and guanidine has a much greater effect than the use of either compound alone.[33]

The two optical isomers of HBB have been synthesized and D-HBB has proven more active than the L-isomer.[24]

So far no experimental studies have been reported of the combined action of D-HBB and guanidine in virus infections in animals or man. HBB and guanidine given alone have shown little effect in poliovirus infections in experimental animals, which is not surprising, because of the high rate at which wild type poliovirus mutates to drug-resistant virus.[34]

Isatin β-thiosemicarbazone

Significant results have been obtained with isatin β-thiosemicarbazone, a substituted hydrazine derivative of a heterocyclic diketone. This compound inhibits the replication of many poxviruses, including human smallpox virus. As with HBB and guanidine, the outstanding action of isatin β-thiosemicarbazone is to inhibit virus-directed protein synthesis,[1] but the effects of isatin β-thiosemicarbazone are different from those of HBB and guanidine. The thiosemicarbazone does not inhibit the replication of viral DNA, which means that the compound does not interfere with the synthesis or function of enzymes required for the replication of viral DNA. The drug also permits the synthesis of some of the viral coat proteins,[11] but the critical fact is that it inhibits the formation of some poxvirus proteins which are essential for the normal morphogenesis and maturation of virus particles. The virus particles that are made in treated cells appear immature in electron photomicrographs.[11]

The prophylactic effects of derivatives of isatin β-thiosemicarbazone in smallpox are well known.[4]

5-Iodo-2′-deoxyuridine

For many years there was no evidence to support the idea that some structural analogs of naturally occurring metabolites might possess selective virus-inhibiting activity. Inhibitors such as

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*Reference Nos. 13, 16, 18, 27, 29.

HBB, guanidine and isatin β-thiosemicarbazone do not act as antagonists of small-molecular precursors of nucleic acids or proteins, nor can they be readily considered on structural grounds as analogs of naturally occurring metabolites.

It has been shown recently, however, that 5-iodo-2′-deoxyuridine (IUDR) possesses therapeutic activity in herpes keratitis in man and in experimental animals, and that in experimental animals it is also effective against vaccinia virus.[25,26] IUDR inhibits the replication of these viruses as well as of several other DNA-containing viruses.

IUDR is a halogenated pyrimidine deoxyriboside. Appropriate kinases convert IUDR to the monophosphate, diphosphate and triphosphate form, and the triphosphate serves, along with the natural nucleoside triphosphates, as precursor for DNA in the reaction catalyzed by DNA polymerase.[10] In careful studies with cells it has been shown that IUDR is incorporated into cellular DNA in place of an equivalent amount of thymidine.[20,28,30] The van der Waals radius of iodine is similar to that of the methyl group in thymidine, which apparently satisfies the enzyme DNA polymerase. The extent of incorporation of IUDR into cellular DNA appears to depend on the concentration of halogenated deoxyuridine, and the inhibition of cell division is similarly concentration-dependent.[6,28] Very low degrees of incorporation are compatible with continued functioning of cellular DNA. IUDR is also incorporated into viral DNA.

No evidence has so far been obtained indicating that IUDR inhibits the multiplication of DNA viruses by interfering with the enzymatic mechanism of the synthesis of viral DNA in the infected cells. It seems probable that inhibition of DNA viruses occurs mainly through the mechanism of incorporation of the structural analog into viral DNA,[31] which results in "lethal viral synthesis." There is reason to believe that the "fraudulent" viral DNA that is made does not function properly; for example, it may direct the synthesis of defective virus coat proteins. The therapeutic effects in the eye may be due to quantitative differences between the virus and the cell with respect to the rates and requirements of DNA synthesis.

In contrast to the utilization of IUDR-phosphate in place of thymidylic acid in DNA synthesis, the fluoro derivative, 5-fluoro-2′-deoxyuridine (FUDR), in its 5′-monophosphate form binds irreversibly to the enzyme thymidylic acid synthetase and thereby blocks the synthesis of thymidylic acid and of DNA.[7,22] The van der Waals radius of fluorine is similar to that of hydrogen in the natural metabolite deoxyuridine. As FUDR lacks therapeutic activity in herpes keratitis, it is clear that the effects of FUDR are strikingly different from those of IUDR both from the chemical and biological viewpoints.

5-Iodo-2′-deoxyuridine was synthesized in a program of study of anti-cancer agents. Its side effects on systemic administration are well known, and there is the possible danger that extensive incorporation of IUDR into DNA could lead to increased mutation rates. It has been suggested that chemotherapeutic trials in which IUDR is administered systemically are justified in potentially lethal diseases of man caused by DNA viruses, including vaccinia gangrenosum, smallpox, simian B virus infection and herpes simplex encephalitis.[5]

Microbial Products

Selective inhibitors of viral multiplication have also been found among microbial constituents or products. As yet, little is known about their mechanisms of action and none have as yet come into clinical use. One difficulty is that these microbial substances are of large molecular weight and have so far not been obtained in pure form. However, as has already been pointed out, the outstanding problem in selective inhibition of viruses is the finding of new selective inhibitors. For most viruses no selective inhibitors are as yet known. We should hope that both synthetic chemistry and microbial fermentation will yield additional inhibitors.

Comment

Recent advances in the study of virus inhibitors have culminated in the demonstration of selective inhibition of virus-directed, virus-specific processes. The first successes in the chemoprophylaxis and chemotherapy of virus diseases have been achieved. It is clear that selective inhibition of viral reproduction can be obtained through a number of very different mechanisms.

One of the particularly promising aspects of the current studies of the mechanisms of action of selective inhibitors is that once the primary sites of action of the inhibitors on virus-specific macromolecules have been precisely defined, this will provide information as to the types of inhibitor-receptor interaction which can give selective inhibition of the viral replicative process. Through such studies new knowledge should evolve of the genetically determined chemical fine structure of viral or virus-directed macromolecules.

The complex question of whether highly active and selective inhibitors of virus multiplication may prove widely useful in the prevention or treatment of virus infections cannot be answered in simple terms. Whether a selective inhibitor is clinically useful depends not only on its potency as a virus inhibitor, but also on the biological characteristics of the virus infection. It is also appropriate to emphasize strongly the need for caution: It is essential to investigate thoroughly the short-term and long-term toxicity of drugs, before clinical application.

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Circulatory Shock

A Symposium on Advances in the Understanding of Mechanisms and Treatment

SHOCK FROM VARIOUS CAUSES, but especially shock following myocardial infarction or during the course of bacteremia or after pulmonary embolization, is a harbinger of death. In spite of the incentive for intensive study of shock occasioned by two World Wars, the relatively common occurrence and disastrous mortality of shock continue to plague medical practitioners, regardless of specialty.

In the past decade there has been an impressive resurgence of interest in the mechanism and treatment of shock. Several clinical research centers have been established for the selective study of patients in shock. The first of these was established at the University of Southern California in the Los Angeles County Hospital. There has been community-wide interest in shock and subjects related to care of the critically ill, in part because of the stimulus provided by the Shock Research Unit in Los Angeles.

This led to the establishment of an annual Symposium on Shock, sponsored by the University of Southern California. During this symposium, a summary of progress in the field of shock is provided by prominent authorities, as well as a review of the work done by members of the Shock Research Unit during the year. The Third Annual Symposium on February 24, 1965, was attended by more than 300 physicians. Newer research relating to the mechanism and treatment of shock and their practical application to the treatment of patients were discussed.

Immunological and Pharmacological Studies in Endotoxin Shock

WESLEY W. SPINK, M.D.*

Studies on brucellosis in experimentally infected animals and in human patients resulted in the formulation of a concept concerning the pathogenesis of endotoxin shock in which the lipo-carbohydrate complex of the brucella cell wall (endotoxin) reacted with antibody in a sensitized host, causing vascular collapse. Subsequent investigations on canine shock with *Escherichia coli* endotoxin supported this concept, and attention was drawn to similarities between endotoxin shock, in which a histamine-like vasoactive substance was liberated into the blood, and anaphylactic shock.[5] It was further demonstrated that the vascular effect of endotoxin was mediated through a heat-labile serum factor (? complement).

The immediate stage of hypotension in canine endotoxin shock is associated with a decrease in complement and a rise in plasma histamine.[4] However, histamine could not be implicated in the later irreversible stage. In fact, an infusion of histamine protected dogs against a lethal dose of endotoxin.

It is generally accepted that the initial hemodynamic effect of endotoxin is vasoconstriction, resulting in peripheral pooling of blood, a reduction in venous return, and a decrease in cardiac output. Besides histamine, other vasoactive substances have been implicated in the genesis of vasoconstriction, including the catecholamines, epinephrine and norepinephrine. Cannon[2] and others have viewed the sympatho-adrenal relationship

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The symposium was held under the auspices of the Shock Research Unit and the Postgraduate Education Division of the University of Southern California School of Medicine, February 24, 1965. This report was compiled and edited by co-ordinator of the course, Max Harry Weil, M.D., Ph.D., director of the USC Shock Research Unit.

Submitted April 21, 1965.

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and the increase in plasma catecholamines as a reflex response to hypotension and an attempt to maintain a favorable flow of blood to the tissues, especially to the heart and brain. More recently, several investigators have maintained that the release of catecholamines is the major cause of irreversibility in endotoxin shock and have advocated the use of adrenolytic agents for treatment.

In an extensive series of experiments on canine endotoxin shock, we have confirmed the observation that a rise in plasma catecholamines, particularly epinephrine, is associated with the appearance of hypotension. Transection of the spinal cord or bilateral adrenalectomy prevents the rise in catecholamines but does not eliminate the hypotensive effect of endotoxin. Animals prepared in this manner succumb to considerably smaller doses of endotoxin. We have concluded that a rise in plasma catecholamines in endotoxin shock represents a protective response to the initial onset of hypotension. However, the possibility still remains that overproduction or sustained secretion of catecholamines contributes to prolonged vasoconstriction, but the precise relationship of these factors in the genesis of experimental shock remains obscure. Little is known about these relationships in human shock. It is not unlikely that several vasoactive substances are released into the blood in endotoxin shock, including histamine, serotonin, bradykinin, catecholamines, acetylcholine and slow-reacting substance, but the primary cause of irreversible shock is not understood.

Our working concept on the pathogenesis of endotoxin shock is that this form of shock represents an immunopharmacological problem. It is for this reason that purified preparations of bacterial cell wall are being investigated in relation to humoral antibodies. The role of the delayed type of hypersensitivity in endotoxin shock is being explored further.

The Coronary Circulation During Shock

ELIOT CORDAY, M.D.*

Cardiac arrhythmias, myocardial infarction and heart failure, resulting in cardiogenic shock, have a similar deleterious effect on the coronary circulation. Hypovolemic shock also depresses myocardial function, as does primary cardiogenic shock. This results in a feed-back mechanism that aggravates the primary condition.

In 1949, the author[3] first demonstrated that coronary flow was decidedly impaired in shock states and that restoration of systemic pressure improved coronary perfusion and function of the myocardium. The first use of vasopressor drugs was in that study, and a short time later they were adopted as routine therapy for hypotension following myocardial infarction.

Investigators have recently cautioned sternly against the use of vasopressor drugs for shock states, postulating that vasoconstrictor effects of the vasopressor may result in an irreversible state of shock. However, our recent studies on animals confirm the anticipated benefit of vasopressor drugs in cardiogenic shock. In addition, they illustrate that the adrenergic blocking agent, phenoxybenzamine (Dibenzyline®), has a dual effect on the coronary circulation. Studies utilizing electromagnetic flow meters revealed that norepinephrine greatly increases coronary blood flow. Phenoxybenzamine, on the other hand, produces an initial reduction in coronary flow with a subsequent increase.

Shock Complicating Myocardial Infarction

HERBERT SHUBIN, M.D.*

Since shock due to acute myocardial infarction is characterized by pronounced reduction in cardiac output and arterial vasoconstriction, clinicians are not agreed on indications for vasoactive amines or their optimal use. In a study of 12 patients in shock following myocardial infarction, metaraminol (Aramine®) and levarterenol (Levophed®) had beneficial hemodynamic action when administered in moderate amounts. However, these drugs had a detrimental hemodynamic effect in larger amounts that increased arterial pressure to "normal" values. When arterial pressure was increased from an average of 57 mm of mercury to approximately 71 mm, an increase in cardiac output averaging 64 per cent above the pretreatment value was observed. Remarkably, this in-

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TABLE 1.—*Vasoactive Agents in Cardiogenic Shock*

No. of Patients	*Agent*	*Modes of Action**	*Arterial Pressure (mean mm Hg)*		*Cardiac Index*
			Control	*Treated*	*Treated*
2	Angiotensin	α	66	78	Down
4	Levarterenol	αβ	55	71	Up
5	Metaraminol	αβ	60	71	Up
2	Mephentermine....	β	56	50	Up
2	Phentolamine	anti α	65	56	Up

*For classification and discussion of vasoactive drugs with alpha and beta activity, see report by Dr. Weil.

crease was associated with a reduction rather than an increase in peripheral arterial resistance. Additional elevation of arterial pressure was not accompanied by a rise in cardiac output. To the contrary, when mean arterial pressure was raised to levels exceeding 90 mm of mercury, cardiac output fell and peripheral vascular resistance increased.

Angiotension raised arterial pressure but did not increase cardiac output. Mephentermine (Wyamine®) and phentolamine (Regitine®) lowered arterial pressure but nevertheless increased cardiac output. Changes in cardiac output in relation to changes in blood pressure with various vasoactive drugs are summarized in Table 1. These studies reemphasize the inadequacy of arterial pressure as a measure of blood flow and confirm the desirability of maintaining mean arterial pressures at levels at least 20 mm of mercury below the preshock level.

Fundamental Differences in Circulatory Effects of Vasoactive Drugs in Treatment of Shock

MAX HARRY WEIL, M.D., PH.D.*

Vasopressor amines are widely used for treatment of acute hypotension and circulatory shock in an effort to restore "normal" or near-normal arterial pressure levels. The circulatory failure clinically regarded as "shock" is primarily a defect of blood flow rather than a deficiency of blood pressure, and vasoconstriction provoked by vasopressor agents may not improve perfusion of vital tissues. The actions of various vasopressor amines in current clinical use were defined in terms of their

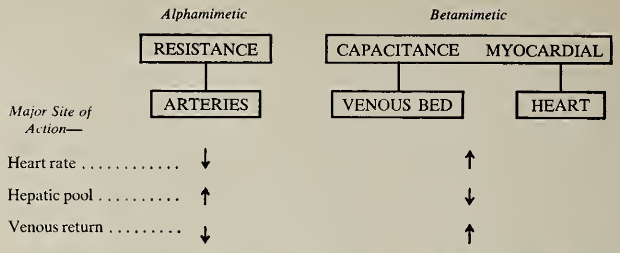

Chart 1.—Major sites of action of alphamimetic and betamimetic vasoactive drugs on the cardiovascular system.

relative effects on the arterial bed (primary resistance vessels), the venous bed (primary capacitance vessels) and the heart. Fundamental differences between vasopressor agents were demonstrated, and the implication that various vasopressor amines have similar hemodynamic actions was disproved. There were remarkable similarities between certain so-called "vasopressor" agents, such as mephentermine (Wyamine®), and "vasodilator" drugs, such as phentolamine (Regitine®).

Detailed studies in human patients demonstrated the applicability of these findings to treatment of circulatory shock. Increased arterial resistance, increased venous pooling and bradycardia were observed with drugs acting primarily on the resistance circuit (alphamimetic). These drugs resulted in a decline in cardiac output. Drugs acting on the capacitance vessels (betamimetic) had an opposite effect. A decrease in arterial resistance, an increase in cardiac output and a cardiotonic effect on the heart, in part reflected by an increase in heart rate, were observed (Chart 1). The effect of betamimetic drugs was indistinguishable from alphalytic phentolamine. This seeming paradox of "vasopressor" and "vasodilator" treatment of shock is largely resolved by recognition of a spectrum of hemodynamic actions (Chart 2) ranging from alphamimetic on one end, simulating aortic crossclamping, to alpha-betalytic on the other end, which simulates spinal transection.

Hyperbaric Oxygenation in Hypoxic Shock States

R. ADAMS COWLEY, M.D.*

Hypoxia is a dominant feature in the pathophysiology of shock. Since the decrease in tissue perfusion and resultant hypoxia is a general mechanism

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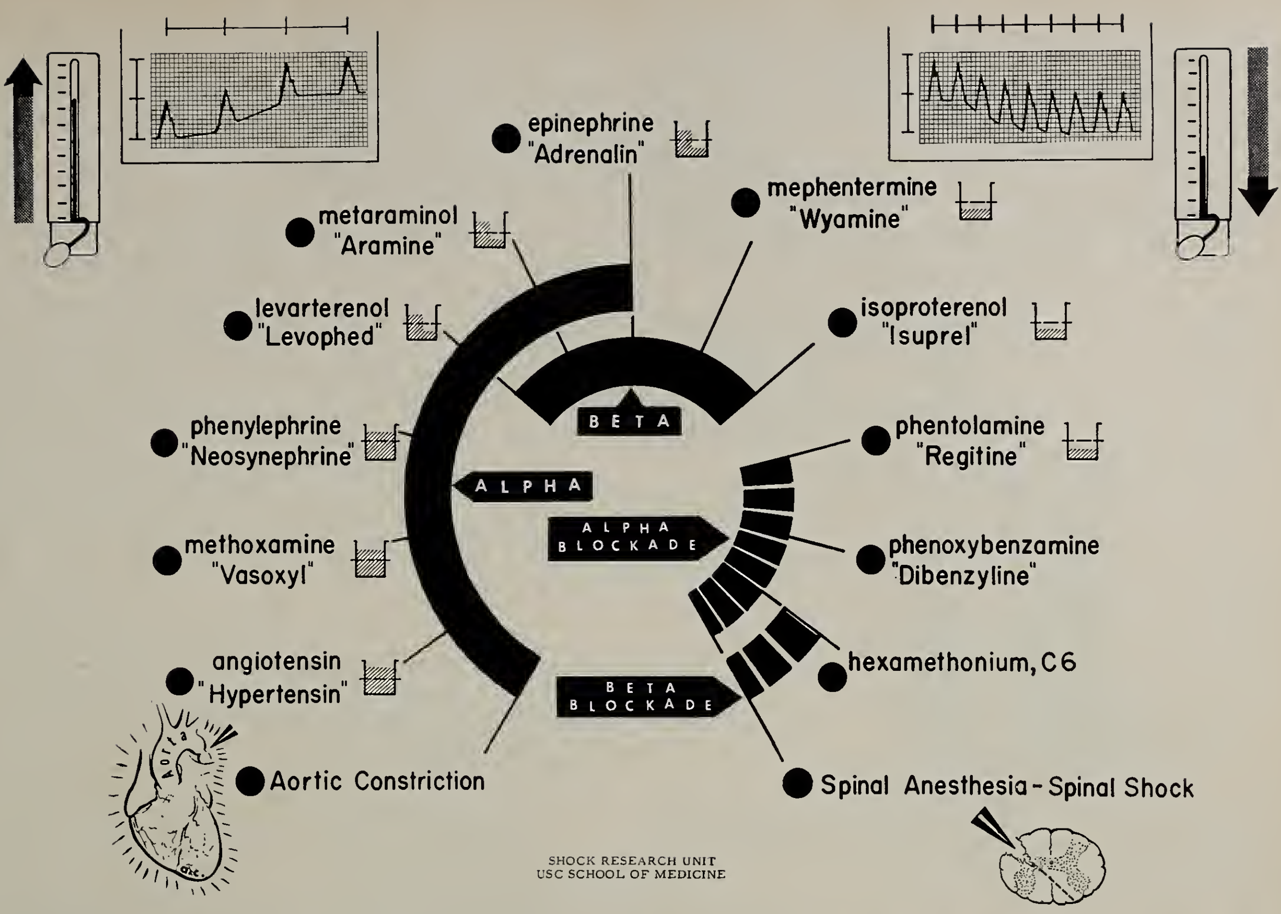
epinephrine
"Adrenalin"
metaraminol
"Aramine"
mephentermine
"Wyamine"
levarterenol
"Levophed"
isoproterenol
"Isuprel"
phenylephrine
"Neosynephrine"
BETA
ALPHA
phentolamine
"Regitine"
ALPHA BLOCKADE
methoxamine
"Vasoxyl"
phenoxybenzamine
"Dibenzyline"
hexamethonium, C6
angiotensin
"Hypertensin"
BETA BLOCKADE
Aortic Constriction
Spinal Anesthesia - Spinal Shock
SHOCK RESEARCH UNIT
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Chart 2.—Concept of a spectrum of hemodynamic actions of various vasoactive drugs initially based on studies in dogs during partial cardiac by-pass. (The beakers indicate changes in the venous pool, the lines representing the normal pool and the shaded areas the response to the drugs. "Stepping" of the shaded area indicates that sometimes the pool is increased, sometimes decreased, depending on the dosage of the drug.) In the studies, cardiac output was controlled by a pump and changes in liver volume were continuously recorded. Angiotensin, methoxamine and phenylephrine increase arterial pressure by constricting arteries and arterioles, reduce heart rate reflexively, and cause a pooling of blood in the venous system. Levarterenol, metaraminol and epinephrine have dual actions. In dogs with constant cardiac output, mephentermine and isoproterenol reduce arterial constriction and cause a net fall in arterial pressure, increase the heart rate, and mobilize blood from venous pools (shown by a decrease in volume in the beaker). Increases in venous return and heart rate account for the greater cardiac output consistently observed in patients. Alpha blockade by phentolamine and phenoxybenzamine results in betamimetic actions simulating small doses of mephentermine and isoproterenol. Ganglionic blockade by hexamethonium combines alpha and beta block. A combination of metaraminol or levarterenol with phentolamine or phenoxybenzamine results in an accentuated betamimetic action equivalent to that following administration of larger doses of isoproterenol.

common to all types of shock, it is not surprising that increased interest is centered on hyperbaric oxygenation (OHP) as a possible means for effective therapy. If the amount of oxygen available to cells were improved sufficiently to compensate for the usual impairment of oxygen transport and delivery during circulatory shock, the problem of hypoxia and its role as the irreversible factor would be largely resolved.

Utilizing standardized preparations, four forms of shock—hemorrhagic, septic, traumatic and shock secondary to pulmonary emboli—were induced in experimental animals. The effects of OHP at oxygen pressures of three atmospheres were measured in terms of survival.

In experimental hemorrhagic shock, the mortality was reduced from 83 to 26 per cent (Chart 3). When this information was reported in 1962,[1] some investigators thought that the reduction in mortality was attributable to the fact that these animals had higher blood pressures during the OHP and a less severe form of shock. Subsequently this possibility was eliminated by study of a group of animals in which the blood pressure was maintained at a constant value during OHP. Although this necessitated additional bleeding and a more profound form of hemorrhagic shock than in controls, a significant reduction in mortality was again demonstrated.

Hyperbaric oxygenation also increased survival in shock after trauma or pulmonary embolization. Biochemical assays indicated that cardiopulmonary function and tissue oxygenation were maintained when OHP was used after pulmonary embolization.

The value of hyperbaric oxygen in treatment of septic shock was less dramatic. Six hours after inoculation of the peritoneal cavity of 10 dogs with fresh suspensions of feces, nine of the 10 died in spite of OHP. In a second group of animals the peritoneal cavity was vented to permit equilibration of the oxygen at the high chamber pressure with the peritoneal cavity. This modified method increased the duration of survival time but not the number of survivors (Chart 4). However, the blood stream in these dogs was cleared of bacteria within one to four hours. In all other groups the bacterial content of the blood stream progressively increased until death. *In vitro* Staphylococci, Escherischia coli and Pseudomonas were greatly inhibited by OHP, suggesting that bacterial growth is effectively curbed if oxygen tensions are sufficiently high at the site of infection.

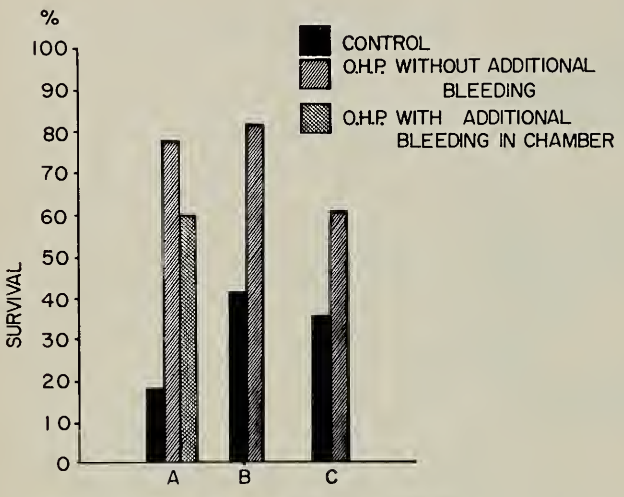

Chart 3.—Effect of hyperbaric oxygenation (O.H.P.) on survival: (a) hemorrhagic shock, (b) traumatic shock, (c) pulmonary embolism.

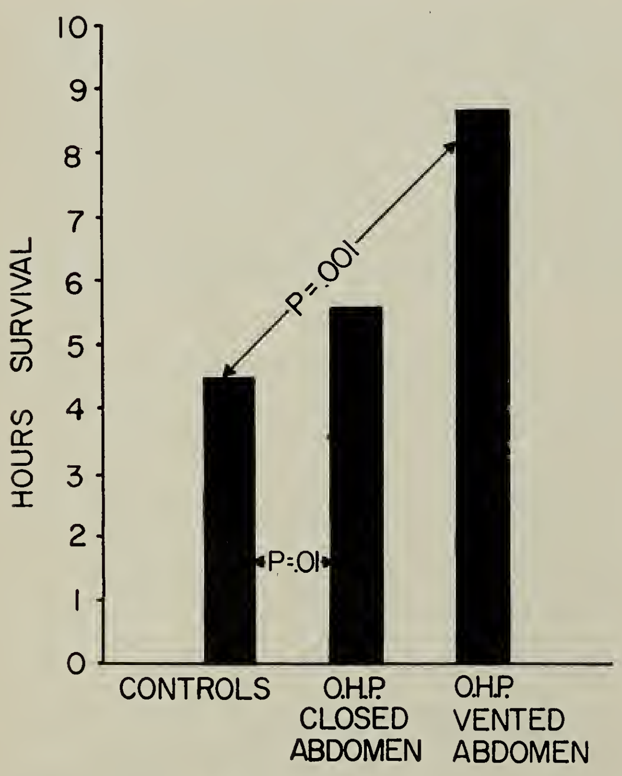

Chart 4.—Survival of animals with septic shock (fecal peritonitis) when treated with hyperbaric oxygenation (O.H.P.).

Results With Phentolamine (Regitine®) In the Treatment of Selected Patients With Shock

EDWARD C. BRADLEY, M.D.*

In dogs, phentolamine (Regitine®) consistently increased venous return while it lowered arterial pressure and peripheral resistance. It appeared likely that this drug had promise for increasing venous return and cardiac output in patients with shock. A total of 37 observations were made on 13 patients with clinical features of shock. Shock was related to bacterial infection in six, fluid loss in two, to a cardiac cause in three and to neurological injury in two. Phentolamine was infused intravenously at an average rate of 0.6 mg per minute for an average duration of 22 minutes. In each trial, cardiac output increased during infusion of phentolamine. With Regitine® alone, cardiac index increased from an average of 2.8 to 3.6 L/min/M^2 (liters per minute per square meter of body surface) on 15 trials in eight patients ($p < 0.001$), and arterial pressure declined from a mean of 73 to 59 mm of mercury ($p < 0.001$). When phentolamine was administered on 22 occasions to five patients in whom arterial pressure had been maintained at low "normal" values by a constant infusion of metaraminol, cardiac index (Chart 5) increased from 2.1 to 3.4 L/min/M^2 ($p < 0.001$). Improvement in systemic blood flow was mani-

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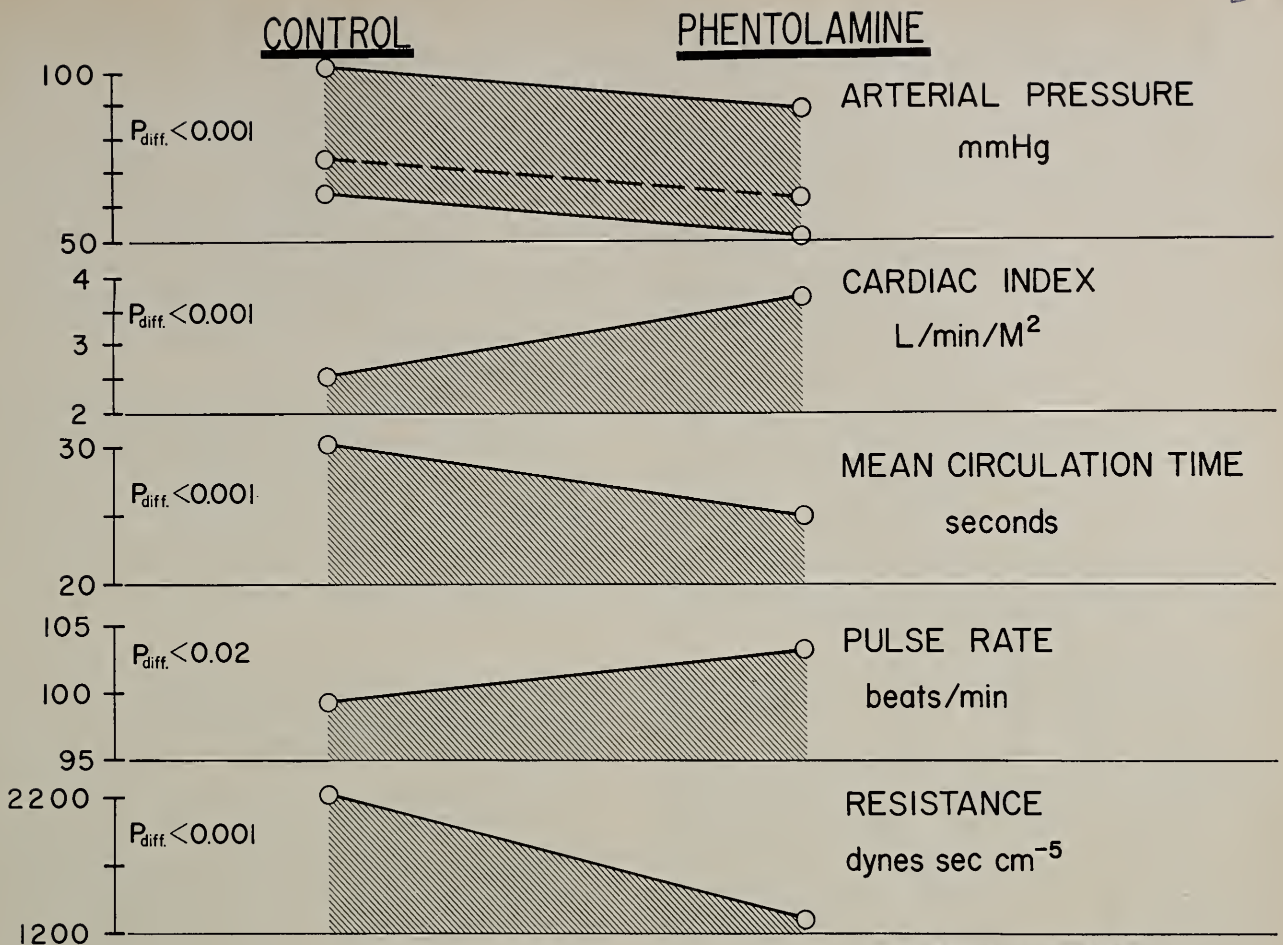

8 pts. 15 trials phentolamine alone
5 pts. 22 trials phent. during ℞ c̄ metaraminal

Chart 5.—Hemodynamic effects of phentolamine in patients with circulatory shock. The mean values for 13 patients are shown.

fested by a reduction in mean circulation time, an increase in peripheral skin temperature and an increase in urine flow.

We conclude that in selected instances an adrenolytic drug may be used in conjunction with, or in preference to, a pressor amine to improve effective blood flow in circulatory shock.

Guiding Volume Repletion in Patients In Shock by Observation of Central Venous Pressure

F. LAIRD FACEY, M.D.*

In guiding fluid repletion in patients in clinical shock, central venous pressure is the single, most useful measurement currently available. Since peripheral venous pressures may be falsely high or low in comparison to central venous pressure, care must be taken to assure that the tip of the catheter used for measurement is in a central vein in the thorax, preferably in the right atrium. The early detection of myocardial decompensation, manifested by a persistent increase in central venous pressure to levels exceeding 15 cm of water, is its principal value. Cardiac overloading is prevented during infusion of fluids by avoiding persistent increases in venous pressure exceeding 5 cm of water.

Central venous pressure is not in itself an index of blood volume. In patients who have lost blood or other fluids, the effects of infusions on central venous pressure are variable. Since central venous pressure reflects the relationship between the volume of blood presented to the heart and the competence of the heart, an increase is due either to overloading with fluid or limited competence of the heart as a pump.

Seven patients with acute circulatory insuffi-

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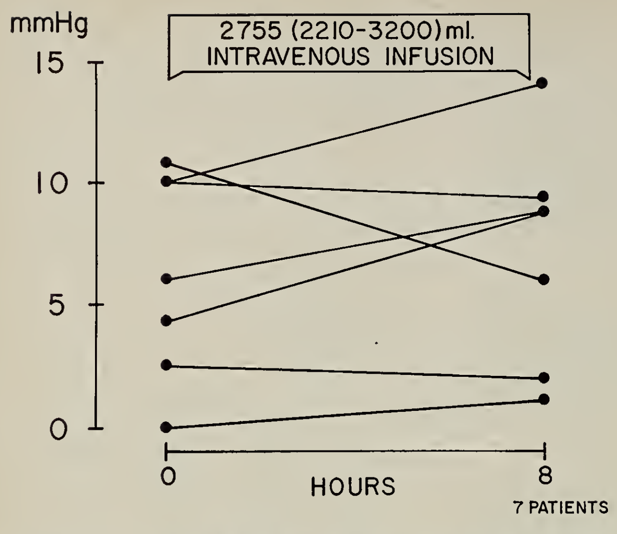

Chart 6.—Changes of central venous pressure after infusion of 2,210 to 3,200 ml of fluid over an eight-hour period in seven patients with circulatory shock.

ciency were successfully treated with fluids in large amounts, averaging 2,700 ml in an eight-hour period without other therapy. Their response to this treatment was a consistent increase in mean blood pressure (72 to 82 mm of mercury), cardiac index (2.6 to 2.9 L/min/M^2) and plasma volume (54 to 64 ml per kilogram of body weight). Changes in venous pressure are shown in Chart 6. The inconsistency in effects on central venous pressure emphasizes that venous pressure is not a measure of intravascular volume. However, it is a reliable indicator of the capacity of the heart to accept additional fluid. We recommend that this technique be routinely used for guiding fluid repletion in patients with clinical shock.

Cerebral Blood Flow in Hemorrhagic Shock

LOUIS L. SMITH, M.D.*

Hemorrhage summons compensatory mechanisms that assure maintenance of blood flow to vital organs, and especially to the brain. The effect of graded hemorrhage on total cerebral blood flow was investigated. In an experiment with dogs, the blood volume was measured and then the animals were bled at intervals of six hours. Eight per cent of the initial blood volume was removed each time. The blood flow through the carotid and vertebral arteries was measured by an electromagnetic flowmeter and related to arterial and central venous pressures, cardiac output and femoral arterial flow as observed before and during hemorrhagic shock. Twenty dogs were studied. In dogs, approximately 70 per cent of total cerebral flow is supplied by vertebral arteries. Vertebral blood flow was maintained at a significantly higher level than femoral blood flow. The larger the hemorrhage, the greater the disparity between vertebral and femoral arterial flow values.

Cerebral blood flow is selectively maintained at the expense of nonvital circulation to muscle and skin. Greater attention should be paid to cerebral function than to blood pressure per se, since the blood pressure is a poor index of cerebral blood flow during hemorrhagic shock.

Newer Methods for Measuring Peripheral Flow in Man

CHESTER HYMAN, PH.D.*

Because shock, or peripheral vascular collapse, is probably associated with a prolonged inadequacy of peripheral blood flow, it follows that a survey of the perfusion of each of the body tissues during shock would provide important data. Sur-

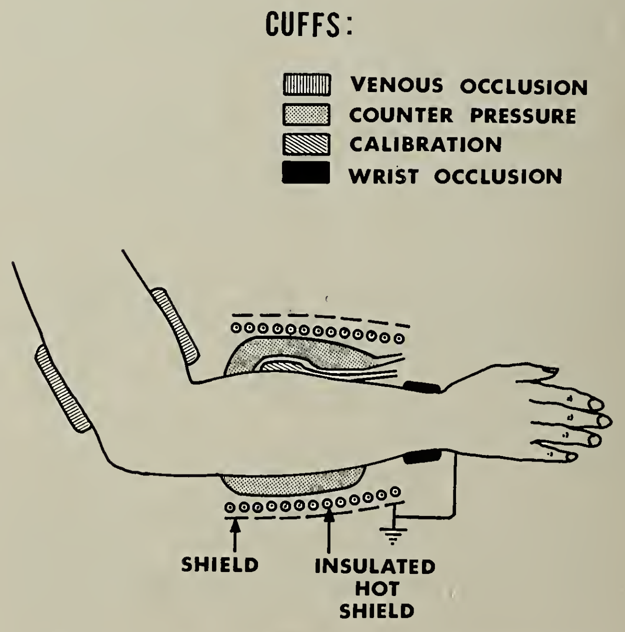

Figure 1.—Use of apparatus for electrocapacitance plethysmography.

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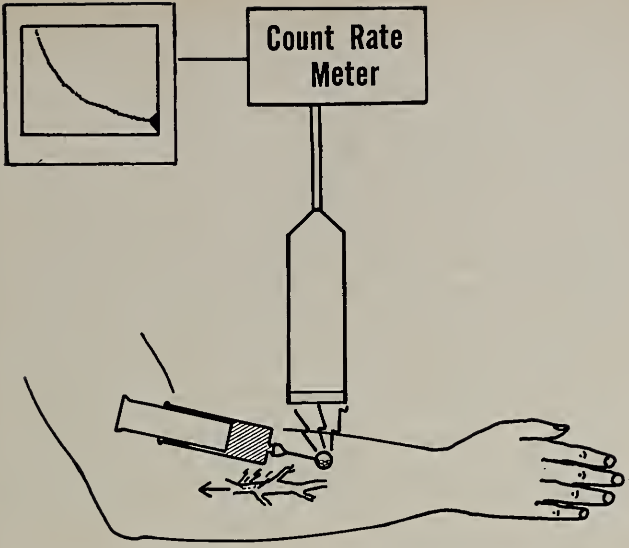

Figure 2.—Tissue clearance method for measurement of peripheral blood flow.

veys of this kind in animal preparations have already been undertaken, but only a few corresponding measurements of circulation in the human in shock have been reported. In general, only those methods should be considered that measure a relatively specific blood flow or perfusion rate and are not traumatic for the already debilitated patient.

Venous occlusion plethysmography is probably the least traumatic method available for measuring blood flow. The recently developed electrocapacitance plethysmograph (Figure 1) provides the additional advantage of leaving the part under study in its normal state: skin temperature, evaporation of sweat from the part and counter pressure on the tissue are unchanged. In addition, the practical advantages of simplicity and ease of handling make this technique the best approach of measurement of blood flow in the extremities.

Blood flow through skin and muscle can easily be separated by an extension of this method. The rate of volume increases after venous occlusion is diminished by pressure applied over the local area. With 25 to 35 mm of mercury in a cuff between the skin and the electrocapacitance screens, blood flow decreases to a level that represents perfusion of deep tissue only. This method has not yet been applied to patients in shock.

The so-called tissue clearance method would also be applied to the evaluation of peripheral circulation in shock (Figure 2). The rate of removal of a small ionic solute from a local injection site in tissue fluid mirrors the rate at which similar molecules are removed from tissues, and provides an estimate of the efficiency of local blood flow. The method involves no trauma, can be directed at a specific tissue, and promises information concerning the physiologically important nutritional flow through the periphery.

Renal Morphology in Patients With Shock

RICHARD E. HOROWITZ, M.D.*

In reviewing the postmortem findings in patients who died on the Shock Ward in 1963, it was found that the most common kidney alteration was the classical "shock kidney," grossly characterized by a pale cortex and a dark red medulla. Microscopically, such kidneys had relatively anemic cortices and pronounced congestion of the vasa recta. Such changes occurred in virtually all patients in shock.

Acute tubular necrosis, also ineptly called lower nephron nephrosis, is thought to be an invariable component of shock. The criteria used for this diagnosis are: (1) patchy necrosis of convoluted tubules; (2) fragmentation of tubular basement membranes; (3) focal acute inflammation; and (4) red cell or heme casts (Figure 3). These changes were observed in only seven of 38 patients with shock and were severe in only three. No cases of renal cortical necrosis were observed, although fibrin thrombi in the glomerular capillaries, the early

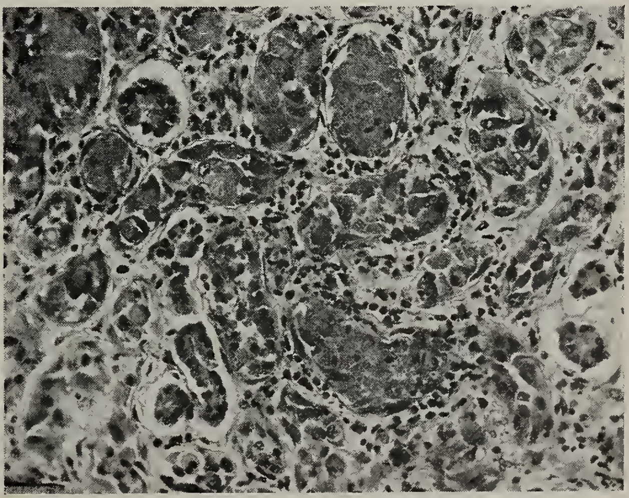

Figure 3.—Acute necrosis of renal tubules. Note necrotic tubular cells, acute inflammation and fragmentation of tubular basement membranes. Hematoxylin and eosin stain, ×250.

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*Assistant Professor of Pathology, University of Southern California School of Medicine.

manifestation of cortical necrosis, were seen in one patient.

The largest single group of patients, nine of a total of 38, had clinical features of shock during, or shortly after, abdominal surgical operation, and these had the highest incidence of acute tubular necrosis (four of the nine patients). No case of clinical shock of less than 12 hours' duration had tubular necrosis. Conversely, tubular necrosis was absent in three patients who were clinically in shock for 48 hours or more. There was no correlation between histological necrosis of tubules and the blood urea nitrogen concentration. Some patients with near normal blood urea nitrogen (BUN) had tubular necrosis, while other patients with BUN over 100 mg per 100 ml had normal kidneys. There was also no obvious relationship between urine flow and acute tubular necrosis.

These observations indicate that the incidence of acute tubular necrosis as a complication of shock is considerably less common than we anticipated and that it is remarkably unrelated to urine flow or blood urea concentration. The data would support the concept that renal failure and oliguria are related to decreased renal perfusion, in part attributable to intrarenal (Trueta) shunts.

The Peripheral Circulation During Shock

HAROLD D. GREEN, M.D.*

Studies were carried out on the comparative behavior of the resistance vessels in skin, kidney, cerebrum and skeletal muscle in dogs during hypotension and shock. Blood flow (electromagnetic-meter) and effective perfusion pressure were measured: (1) during local hypotension produced by graded compressions of the arterial supply to the organ; (2) during systemic hypotension produced by graded withdrawal of blood in steps of 5 ml per kg of body weight until mean arterial pressure was reduced to 35 to 40 mm of mercury; (3) during hypotension maintained at 35±5 mm of mercury for 1.0 to 2.5 hours by additional withdrawals of blood as required; and (4) during the "irreversible" phase of shock (Chart 7). "Irreversible" shock occurred when the blood pressure fell further unless blood was reinfused. When the "uptake" of blood reached 5 ml per kg, all remaining blood was returned to the animal. Arterial pressure rose and usually approached the control level, but then declined progressively until the animal died.

In the cerebrum, kidney and skeletal muscle, blood flow was usually maintained at near normal levels by local autoregulation in the face of declining perfusion pressure. However, vasoconstriction occurred in kidney and skeletal muscle, overpowered the autoregulation, and severely reduced flow in these organs as well as in the skin. In skeletal muscle, vasoconstriction was mediated by neural pathways, whereas both humoral and neurogenic mechanisms operated in the skin. Cerebral blood flow was maintained even though systemic arterial pressure decreased.

Vasodilation occurred in skeletal muscle and the cerebral bed during development of "irreversibility." This vasodilation in skeletal muscle may be an unfortunate decompensatory change accounting for the final progression of shock.

Reports from the USC Shock Research Unit on Practical Aspects of Management of the Critically Ill

Miss Martha Kawabe, R.N., Head Nurse in the Shock Research Unit, discussed clinical management and research on the critically ill. She described the emergence of nursing in the computer age and indicated the remarkable efficiency and accuracy obtained with the aid of the computer in measuring arterial pressure, venous pressure, pulse rate, heart rate, urine output and other vital functions. The possibility of using the computer to regulate the rate of infusions and to initiate automatic heart pacing was reviewed. The implications of such medical technologic changes as they affect the training of nursing personnel were apparent.

David G. Stadelman, a mathematician who formerly served as principal programer of the Shock Research Unit, discussed the interphase of computer technology and medicine and the feasibility of installing a computer in a hospital environment to assist in the management of patients. He demonstrated the potential value of automatic plotting and logging to relieve nursing and medical staffs of the time-consuming tasks that interrupt more direct care of the patient. The tremendous potential of improving understanding of the patient's condition by automatic presentation of information

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*Gordon Gray Professor and Chairman, Department of Physiology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem.

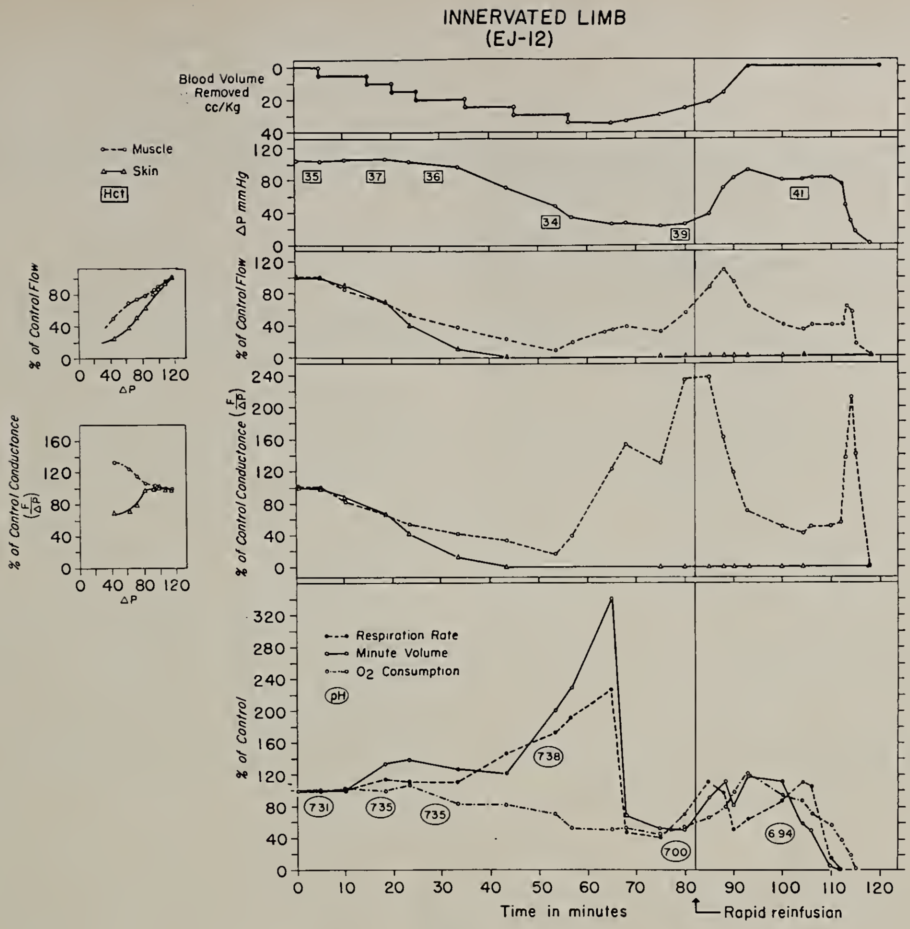

Chart 7.—Changes in muscle and skin blood flow and associated measurements during bleeding.

to the physician in an orderly fashion, including data which would require many hours of calculation, was also presented.

Dr. Leonard Rosoff, Associate Professor of Surgery and a Co-principal Investigator in the Shock Research Unit, summarized the progress in the Unit during the past four years. He indicated the radical change in concept of the mechanism of bacterial shock, which is no longer regarded as a problem of "vasomotor collapse" but rather a problem of venous pooling and a reduction in venous return. The improved understanding of mechanisms has allowed for improved means of treatment, such as the use of corticosteroids which mobilize blood from pools and improve cardiac output. He referred to the improved understanding of the clinical value of venous pressure, as described by Dr. Facey. In commenting on the fundamental causes of shock, Dr. Rosoff referred to recent work in the Shock Research Unit which showed that in some patients, particularly patients with hepatic cirrhosis, the cardiac output may be normal or high, but the actual amount of blood available to nourish vital tissues is decreased. It is this decrease in essential blood flow to vital tissues rather than total flow—that is, cardiac output—that accounts for the progression of shock.

Dr. Donald B. Doty, a Resident in Surgery at the Los Angeles County Hospital, reviewed the role of blood volume and indicated the deficiency of peripheral hematocrit as a measure of red cell volume in the body. A very interesting observation concerned differences in the hematocrit in various parts of the body. Preliminary studies revealed that capillary hematocrit was elevated in comparison with central venous and arterial hematocrit in patients who were unequivocally in circulatory shock.

Dr. Milton L. Smale, a Resident in Obstetrics and Gynecology at the Los Angeles County Hospital, reported on a study of four patients with septic abortion complicated by shock. He indicated that prompt removal of infected products of conception and close attention to treatment of bacteremia with antibiotics and pharmacological amounts of corticosteroid hormone have been valuable guide lines for treatment.

Summary

With intensive study of the patient, supplemented by careful observations in the experimental laboratory, we are now led to a greatly improved understanding of the mechanisms of shock. The dilemma of vasopressor and vasodilator drugs is being resolved. Special techniques for treatment, including hyperbaric oxygenation, use of large doses of corticosteroids, and selective control of infections due to gram-negative enteric bacteria, are promising. Computers are making their way into hospitals and have great potential for assisting medical and paramedical staffs in the efficient accumulation of information. They have the advantages of speed and accuracy and, to a limited extent, they will be able to control simple mechanical functions, such as the "drip" rate of intravenous infusions.

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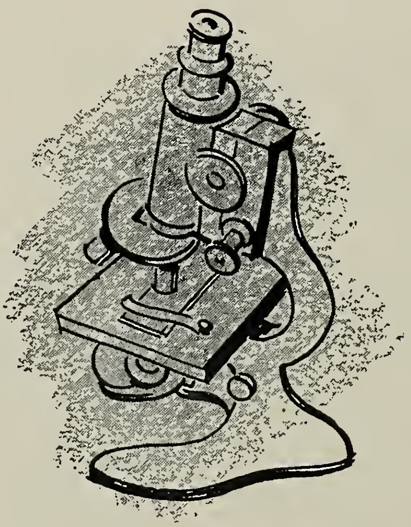

Cerebrovascular Occlusive Disease

Experience with Panarteriography in 300 Consecutive Cases

F. WILLIAM BLAISDELL, M.D., ALBERT D. HALL, M.D.
ARTHUR N. THOMAS, M.D., STEVEN J. ROSS, M.D.
San Francisco

■ *Three hundred patients with cerebrovascular occlusive disease have had cerebral angiographic examination at the Veterans Administration Hospital, San Francisco, in the last five years. The present technique consists of preliminary visualization of the aortic arch and the major extracranial branches, followed by selective study of the subclavian and carotid arteries as necessary for evaluation of the intracranial circulation.*

Nine major complications occurred (an over-all incidence of 3 per cent). Two patients died after angiography and seven had major neurologic deficits persisting for more than 24 hours. Three of these patients had permanent damage, but four recovered completely.

One-third of the patients had extracranial disease and one-third had intracranial disease. No significant lesion was found in the remainder. In the 212 patients with lesions, multiple lesions were common, the average number being three. Six patients had brain tumors and five had aneurysms.

The mechanism of the stroke could be ascertained readily in most of the patients, but the extent of the disease and the resulting symptoms varied considerably. Several patients with occlusion of most of the cerebral vessels had minimal symptoms, while others had catastrophic symptoms but only minimal findings at arteriography.

CEREBROVASCULAR OCCLUSIVE DISEASE is the third leading cause of death, yet our understanding of many of the fundamental aspects of this condition, etiologic and physiologic, still is incomplete. Although at least one-third to one-half of the lesions that cause stroke are located in the neck,[5] the significant etiologic role of the extracranial arteries in stroke has been recognized only since the introduction of arteriography, which permits visualization of the entire cerebrovascular tree.[1,2,8]

Since July 1960, we have been using cerebral arteriography frequently in patients thought to have cerebrovascular disease. Our experience with the first 100 patients in whom cerebral angiography was used for diagnosis of stroke has been reported.[1] Our present series is made up of 300

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consecutive cases, including those in the first report. In all of these patients several vessels were examined, since study of individual vessels is usually inadequate in the evaluation of patients with stroke. In this study we measured the risks involved in panarteriography against the benefits, to assess the value of the procedure.

Technique

The details of the technique of examination of individual cerebral vessels have been reported.[1] To obtain maximum information about the cerebrovascular tree while avoiding excessive discomfort to the patient and minimizing the risks involved in injection, the vessels should be studied in an orderly sequence.

The usual method of examination at present consists of retrograde percutaneous catheterization of the brachial artery. Catheters are passed directly into the ascending aorta. Aortic injection gives a good preliminary view of the entire extracranial cerebrovascular system and permits localization of the disease in the extracranial vessels. Needles then can be introduced in the individual arteries as necessary, thus avoiding sites of maximum arteriosclerotic involvement.

An injection of 50 ml of an 80 per cent solution of sodium iothalamate* is made into the ascending aorta under 200 to 300 pounds pressure through a catheter with an internal diameter of 0.046 to 0.063 inches. Multiple exposures are taken at one-second intervals with the patient in the right posterior oblique position. A film measuring 11 x 14 cm is positioned so the lower margin is at the sternal angle. A second injection is made in the anterior-posterior projection. The film extends from the level of the take-off of the vertebral artery to the top of the cranium. If these films are satisfactory, the catheter is withdrawn into the right subclavian artery and 30 ml of a 60 per cent solution of methyl golucamine diatrizoate† is injected into the subclavian artery two to three cm distal to the origin of the vertebral artery. Multiple films are taken in the Towne position for intracranial visualization of the vertebral-basilar system. If contrast is adequate in the intracranial portion of the right carotid system by retrograde filling of the innominate artery, the injection is repeated with the film exposed in the lateral position, which completes the examination of the right carotid artery.

Percutaneous puncture of the left common carotid artery is then performed and anterior-posterior and lateral carotid arteriograms are obtained. If visualization of the right carotid system is inadequate, direct injection of the right carotid artery is necessary. Similarly, inadequate visualization of the basilar system from the right vertebral injection requires left vertebral arteriograms obtained by percutaneous catheterization of the left brachial artery.

If this method is not feasible because of the nature of the disease, alternative methods of initial visualization of the aortic arch can be used. If disease in vessels of the upper extremity makes catheterization difficult, the catheter can be passed retrograde from the femoral arteries and the tip can be positioned in the ascending aorta. In this case, both carotid arteries must be punctured percutaneously and at least one study of the subclavian artery should be done to visualize the basilar artery.

Occasionally the patient with extensive cerebrovascular disease has associated arteriosclerosis of the lower extremities. In this instance, an adequate screening examination can usually be accomplished by injection of a contrast agent into one of the great veins in the chest. The best technique for visualization of the aortic arch via the venous route is percutaneous or direct catheterization of the exposed basilic vein in the antecubital fossa or the external jugular vein in the neck. A catheter with an internal diameter of 0.063 inch is passed downward into the superior vena cava near the right atrium. A solution of 80 per cent sodium iothalamate, 1 ml per kg of body weight, is injected under pressure. The patient is told to continue breathing during and immediately after the injection in order to prevent the Valsalva maneuver and obstruction of the flow of dye through the lungs.

Usually, multiple films are made, beginning ten seconds after injection, and six to eight films are taken in the right posterior oblique position two seconds apart. If the degree of contrast in the cerebral vessels is adequate, a similar picture is taken in the anterior-posterior projection as described for direct visualization of the arch.

Complications

Deaths and major complications (Table 1). In the present series, two deaths were directly related to arteriography. The first, in a 70-year-old pa-

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*Angio-Conray, a product of Mallinckrodt Chemical Works, St. Louis.

†Renografin-60, a product of E. R. Squibb & Sons, New York.

TABLE 1.—*Deaths and Major Complications of Panarteriography*

Complication	*Duration and Residual Effects*
Convulsions and cardiac arrest	Resuscitation unsuccessful; patient died 30 minutes after injection
Left hemiparesis and left homonymous field defect	Patient died 3 days after angiography
Hemianopsia and mental deterioration	Permanent mild visual defect and mental impairment
Severe vertigo	Complete recovery in 10 days
Dysarthria, vertigo and lethargy	Complete recovery in 10 days
Dysarthria and mental depression	Recovery, except for slight residual effect, in 10 days
Right hemiparesis	Recovery of leg function after 3 weeks; permanent residual weakness of arm and face
Convulsions and progression of previous left hemiparesis	Permanent increase in spasticity, left side
Convulsions and somnolence	Gradual complete recovery in 3 days

tient, resulted from extravasation of dye after injection of the right subclavian artery near the orifice of the vertebral artery, resulting in temporary closure. The patient had a major stroke and died a week later. At autopsy the right vertebral artery was the only patent extracranial vessel. The second death was in a 76-year-old patient. The only palpable pulse was in the right carotid artery. No vessels were palpable in any of the four extremities. Injection into the right carotid artery was followed by convulsion, temporary anoxia and ventricular fibrillation. Attempts at cardiac resuscitation were unsuccessful. At autopsy all the cerebral vessels were occluded and none of the major coronary arteries were open. Both of these patients had been disabled by their disease. The first had progressive blindness related to retinal ischemia following occlusion of both carotid arteries. The second had progressive loss of vision, episodes of syncope and mental deterioration.

The major complications in this series consisted of cases of major neurologic changes which persisted for more than 24 hours. Vascular occlusions which did not result in neurologic changes were not considered to be major complications since in none of these 300 cases did occlusion of a vessel threaten life or limb. Pneumothorax was not considered a major complication, since it was looked for routinely in the supraclavicular subclavian studies and in all cases of pneumothorax the complication was treated promptly, with negligible patient morbidity. Seven patients had major neurologic complications, but only three of them had a permanent neurologic deficit. The mortality rate in the series was 0.67 per cent (two out of 300) and 2.3 per cent of the patients had major complications (seven of 300), or a total rate of 3 per cent for death and major complication.

Minor complications (Table 2). In 63 cases, intramural or extravascular injections were followed by discomfort to the patient or by difficulty in interpretation of the arteriograms. Significant hematomas occurred after 47 of the individual vessel studies. The minor neurologic complications consisted of 19 instances of convulsion and 18 transient neurologic deficits. All the convulsions occurred immediately following injection and were most common in examinations of the carotid artery. The 18 minor neurologic deficits consisted of neurologic changes which lasted less than 24 hours. These included three cases of transient hemiparesis, two of temporary blindness, three of somnolence, seven of aphasia or dysphasia, and one each of paresthesia, diplopia and vocal cord paralysis.

Pneumothorax occurred in 24 patients, but the only time it posed a serious threat was in a patient with bilateral involvement. Pneumothorax was a frequent complication of supraclavicular subclavian puncture but was relatively infrequent in studies of other arteries. In 14 patients vascular occlusion occurred which lasted more than 48 hours. Twelve of these patients had brachial artery occlusions after retrograde brachial catheterization and two had femoral occlusions after catheterization. In one patient a small fistula of the brachial artery-vein occurred, requiring surgical correction. The 15 miscellaneous complications consisted of nausea, headache, postural hypotension and syn-

TABLE 2.—*Minor Complications of Panarteriography*

Complication	*Number of Patients*
Extravasation	63
Hematoma	47
Minor neurologic deficit	37
Pneumothorax	24
Vascular occlusion*	15
Allergic reaction	8
Miscellaneous†	15

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*Includes one traumatic arteriovenous fistula.
†Including nausea, headache, hypotension, syncope.

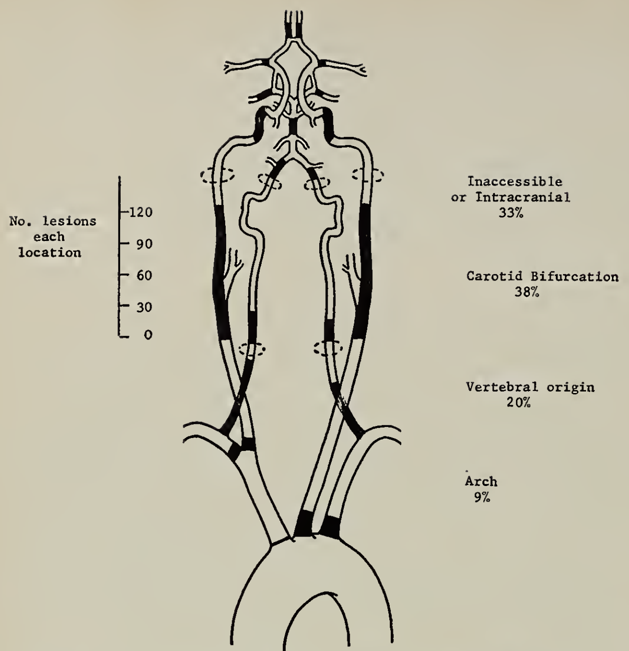

Figure 1.—Location and incidence of significant atherosclerotic lesions. The length of the dark area at each location (measured against the scale at left) corresponds to the number of lesions detected by arteriography in this series.

cope. Only eight patients had minor allergic reactions, consisting mostly of urticaria.

Results

Cerebrovascular occlusive disease was the primary diagnosis before angiography in the 300 patients in this study. The distribution of the 567 lesions considered to be significant is shown (Figure 1). A significant lesion was considered to be one that narrowed the lumen of the vessel by 30 per cent or more. Roughly one-third of the patients had intracranial lesions, one-third had extracranial lesions and in one-third no significant atherosclerotic lesions were visible in the cerebrovascular tree. The 212 patients with definite arteriographic evidence of disease had an average of three lesions each. Eighty-four of the patients with lesions had both intracranial and extracranial disease. Five patients had aneurysms and six had brain tumors.

Visualization of lesions on these arteriograms gave valuable specific information concerning the mechanism of the stroke, including the detection of unsuspected cardiac emboli, emboli from arteriosclerotic plaques or fibrin emboli from proximal ulcerated lesions in the cerebrovascular tree. Also found were atherosclerotic stenosis of vessels, complete atherosclerotic occlusion and hemorrhagic dissection under atherosclerotic plaques with partial or complete occlusion. In many instances the conclusions drawn from these arteriograms were verified at operation or autopsy. These specific findings at arteriography were frequently useful in directing therapy. The specific value of arteriography is demonstrated in the following case reports.

Case Reports

CASE 1. A 54-year-old man had a seven-year history of paralysis of the right side and severe claudication in the legs. He was prematurely senile, had expressive aphasia and his replies were limited to single words. He had right central facial weakness and spastic right hemiparesis which was most severe in the upper extremity. The carotid pulse was weak on the right side and absent on the left. Blood pressure in the right arm was 170/80 mm of mercury and could not be determined in the left arm. Preliminary visualization of the aortic arch by injection of dye into the superior vena cava showed stenosis of the innominate bifurcation, complete occlusion of the right internal carotid artery, complete occlusion of the left common and internal carotid arteries and complete occlusion of the left subclavian artery (Figure 2).

Discussion. The patient's major disability was progressive mental deterioration after a severe cerebrovascular accident seven years previously. If angiography had not been performed it might have been assumed that these changes were solely due to occlusion of the left carotid artery, since no pulse was palpable in this vessel. Most of the patients with generalized deterioration resulting from cerebrovascular disease had simultaneous occlusion of most of the cerebral vessels. In this patient the only patent vessel was the right vertebral artery. In addition, the blood flow in this artery was compromised by stenosis of the innominate artery and blood flow to the brain was further limited since the left vertebral artery provided the principal collateral to the arm. Arteriograms demonstrated that the left subclavian artery filled from injection of the right vertebral artery through retrograde flow in the left vertebral artery; thus the arm was diverting flow from the brain—"subclavian steal."[3,10] After complete angiography revealed the severity of the patient's disease, surgical therapy was directed at improving blood flow in the vertebral arteries. An excellent immediate result was obtained. His aphasia and mental alertness improved noticeably and instead of vegetat-

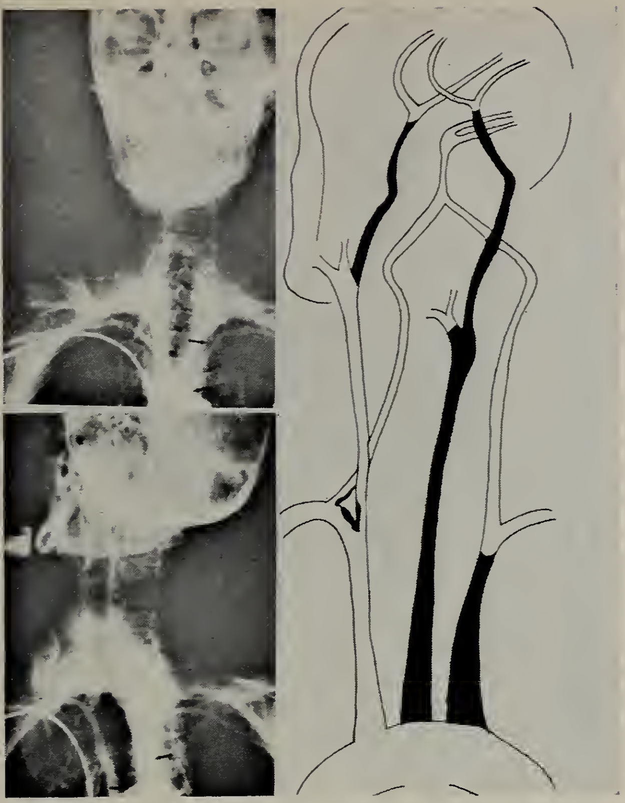

Figure 2 (Case 1).—Venous injection of the aortic arch, showing stenosis of the innominate bifurcation, complete occlusion of the left common and internal carotid arteries and complete occlusion of the left subclavian artery. The left vertebral artery fills retrograde from the right vertebral.

ing in bed he became ambulatory and able to care for himself. Follow-up of one year indicates the initial improvement has been maintained.

Complete cerebral angiography permits the vascular surgeon to select the lesion or lesions most amenable to surgical treatment. We have found the circle of Willis to be hemodynamically competent. Restoration of blood flow in the carotid system will usually relieve arterial insufficiency of the brain stem, and successful surgical treatment of the vertebral artery will improve function in the portion of the brain ordinarily supplied by the carotid arteries.

Case 2. A 56-year-old man was admitted because of transient hemiplegia, aphasia and sudden onset of vertigo just before admittance. The blood pressure was 170/85 mm of mercury in both arms and there were bilateral carotid bruits. He had right facial weakness and slight weakness of the right arm. Arteriograms showed a plaque at the origin of the left carotid artery and a filling defect in the middle cerebral artery on the same side which resembled an embolic lesion (Figure 3). As a result of these findings long-term anticoagulation therapy was initiated. Follow-up at six months revealed no symptoms or signs of recurrent embolism.

Discussion. Arteriosclerosis is predominantly a disease of large and medium-sized arteries. Most of the catastrophic symptoms occur following sudden occlusion of a previously patent artery. In our experience, many of the occlusions of the middle cerebral arteries found at arteriography or autopsy appear to be of embolic origin and investigation of the neck vessels at operation or autopsy reveal associated ulceration of the corresponding vessel in the neck.[6] These embolic fragments may produce catastrophic symptoms. The associated thrombosis of the vessel occluded by embolus may obscure the nature of the lesion. Other embolic lesions may arise from bits of fibrin which form in irregular areas on the surface of a proximal arteriosclerotic plaque. Subsequent cerebral arteriograms or retinoscopy often reveal that these fibrin emboli have disappeared without a trace.[4,8] This was true in several patients in this series in whom long-term follow-up was possible.

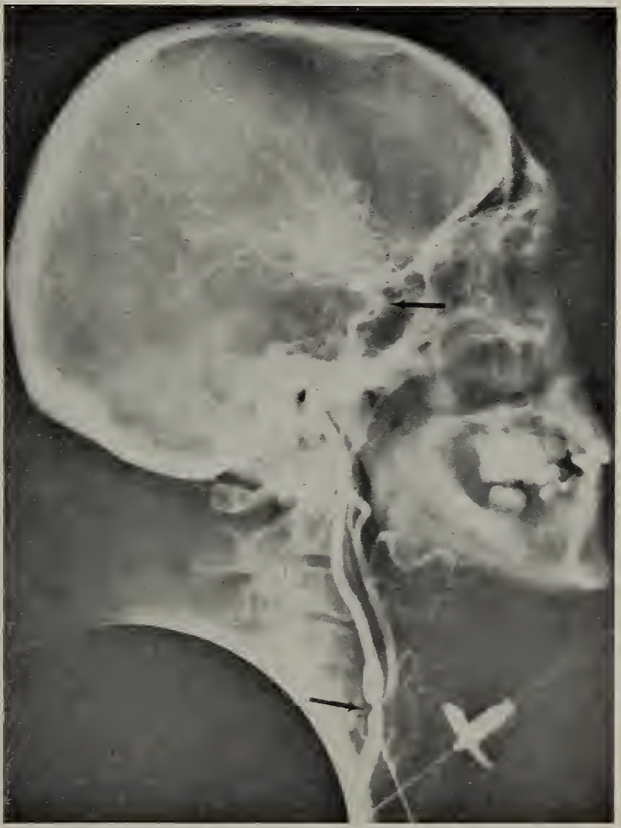

Figure 3 (Case 2).—Proximal atherosclerotic plaque on the origin of the right internal carotid artery with embolization to the distal intracranial portion of the internal carotid artery.

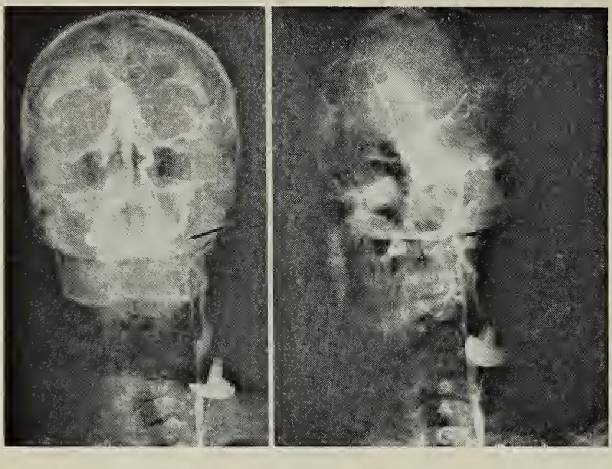

Figure 4 (Case 3).—Left arteriogram taken immediately after onset of right hemiplegia (left frame) shows nearly complete obstruction of the internal carotid artery. The frame at right shows a right arteriogram taken one month later, showing disappearance of the lesion.

Case 3. A 51-year-old electrician was entirely well until 36 hours before admission, when he had a sudden onset of blindness in the left eye and weakness progressing to complete paralysis of the right arm and leg. The blood pressure was 120/80 mm of mercury in both arms. Pulsations were normal in the neck vessels and he had a bruit over the bifurcation of the left carotid artery. Neurologic examination demonstrated slight residual weakness in the right arm and leg, but significant improvement had occurred since the preadmission examination 24 hours previously, immediately following onset of symptoms. The pressure of the left retinal artery was half that in the right. Arteriograms (Figure 4) showed no abnormality except for nearly complete occlusion of the left internal carotid artery at the base of the skull; follow-up arteriograms a month later showed the artery to have spontaneously returned to normal (Figure 4).

Discussion. The patient recovered almost completely from the stroke although no specific therapy was given. Exploration of similar lesions indicates that acute strokes may be caused by dissection of blood under an atherosclerotic plaque, followed by sudden, complete occlusion of the vessel and distal thrombosis. In this instance the immediate acute obstruction was not complete and permitted some flow of blood past the lesion; the natural fibrinolytic mechanism of the body apparently resulted in reabsorption of the clot and readherence of the plaque to the artery.[9] Follow-up arteriograms a month after the initial episode would have been considered to be "negative." Although it is difficult to prove, it seems likely that such lesions may have been present in a significant number of patients with stroke in whom angiographic examination showed no abnormality.

Case 4. A 53-year-old truck driver was admitted for evaluation of dizziness and blurring of vision of one and a half years' duration. He had been treated for atrial fibrillation and mild congestive failure since the onset of the symptoms. He was referred for cerebrovascular evaluation because of the absence of blood pressure in the left arm. After detailed questioning he recalled that he had had a slight weakness in the left hand for a year and three episodes of loss of consciousness. The primary complaints were shortness of breath, dyspnea and frequent episodes of ankle edema, for which digitalis and diuretics had been given. The blood pressure was 175/100 mm of mercury in the right arm and 120/100 in the left. Carotid pulsations were decreased and bruits were present over both carotid bifurcations. The patient was mentally alert and the neurologic examination was essentially negative. Four-vessel cerebral arteriography showed complete occlusion of the

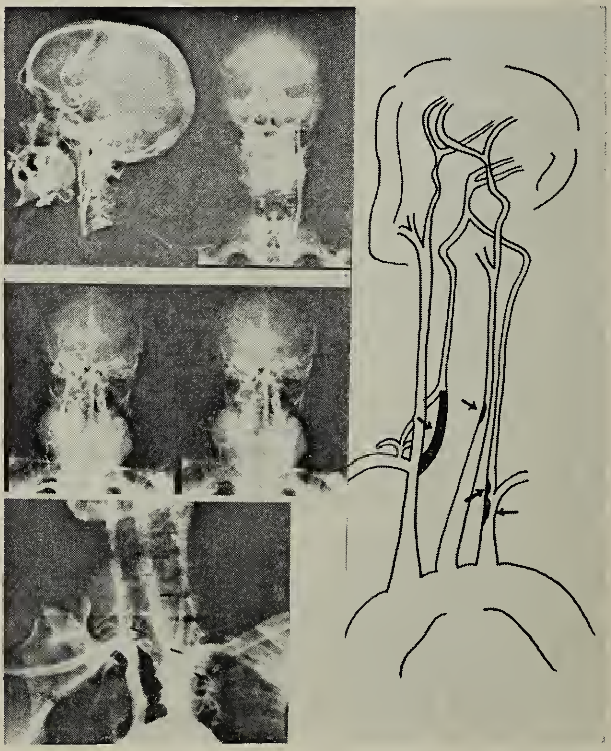

Figure 5 (Case 4).—Standard complete arteriograms. Film at top is arteriogram of left carotid artery; Center film shows right vertebral and carotid arteries and the one at the bottom shows its aortic arch. Together they show complete right vertebral occlusion, a 40 per cent stenosis of the left common carotid artery and pronounced stenosis of the left subclavian and left vertebral arteries.

right vertebral artery, stenosis of the left common carotid artery, almost complete occlusion of the left subclavian artery and stenosis of the origin of the left vertebral artery (Figure 5). Surgical correction of the left subclavian stenosis results in disappearance of symptoms through one year of follow-up.

Discussion. At first the symptoms were believed to be of cardiac origin. The decreased blood pressure in the left arm pointed to the possibility of concomitant cerebrovascular disease, and the findings at arteriography readily explained the cause of the brain-stem ischemia. The first manifestation of cerebrovascular disease frequently occurs at the time of onset of cardiac disease. Transient or permanent decreases in cardiac output may give rise to cerebrovascular symptoms of minor to catastrophic degree. Conversely, a stroke may be the first evidence of certain types of cardiac disease, such as a "silent" myocardial infarction. Both systems should therefore be evaluated simultaneously.

CASE 5. A 63-year-old retired engineer was admitted with a history of left hemiparesis of 24 hours' duration. He had had transient episodes of left hemiparesis that had begun eight months previously. The blood pressure was 100/70 mm of mercury in both arms. Neck pulses were normal and no bruits were present. Bilateral arteriograms of the carotid artery demonstrated a filling defect at the bifurcation of the right carotid artery and a smaller filling defect in the middle cerebral artery on the same side (Figure 6). The patient's condition deteriorated steadily after admission. He was comatose when arteriograms were obtained. Embolectomy was done immediately after arteriography, but he died a month after admission.

Discussion. The patient's symptoms were caused by acute embolism at the carotid bifurcation. The origin of the embolus was presumed to be the heart. Before arteriographic examination the tentative diagnosis was atherosclerotic occlusion of the cerebral vessels. Arteriography revealed an unequivocal embolus at the carotid bifurcation. If the lesion had not been catastrophic and the patient had recovered, more attention would have been directed toward the cardiac disease and proper therapy to prevent further embolism.

CASE 6. A 59-year-old building inspector was admitted because of weakness of three day's duration in the left side of the face and the left arm and leg. Blood pressure was 160/100 mm of mercury in both arms. Neck pulsations were normal and no bruits were noted. He had mild weakness of the left side of the face, left arm and left leg. Arteriograms of the right and left subclavian and carotid arteries were obtained. No occlusive disease was seen and the only significant finding was a large intracranial aneurysm (Figure 7). Although surgery was recommended the risks were emphasized and the patient declined further treatment.

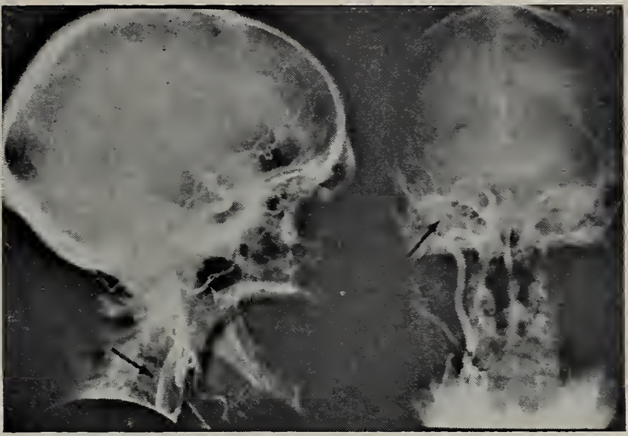

Figure 6 (Case 5).—Large embolus at the bifurcation of the right common carotid artery and small embolus in the right middle cerebral artery. (The heart was the presumed site of origin.)

Discussion. Angiography had not been performed previously in this patient because of his age and evidence of systemic arteriosclerosis. This made the diagnosis of an atherosclerotic occlusive lesion most likely. Once the pathologic findings were demonstrated, however, craniotomy was the recommended treatment of this dramatic aneurysm.

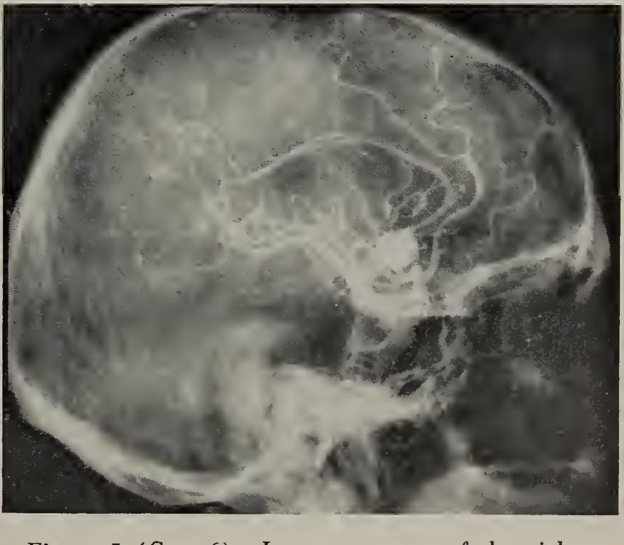

Figure 7 (Case 6).—Large aneurysm of the right anterior cerebral artery, not suspected before angiography.

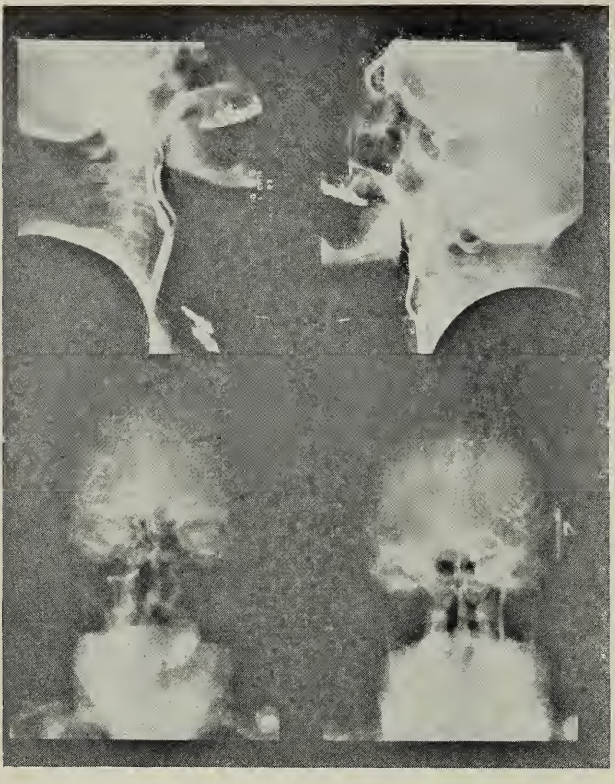

Figure 8 (Case 7).—At top are preadmission lateral views of right and left carotid arteries, showing stenotic lesions at the origin of both internal carotid arteries.

Films at bottom, repeated arteriograms including anterior-posterior views show shift of anterior cerebral arteries to the right and depression of the left middle cerebral artery consistent with a frontoparietal brain tumor.

CASE 7. A 70-year-old retired man was admitted for surgical treatment of carotid stenosis. Right hemiparesis had occurred seven days previously. Carotid arteriograms done before admission showed lesions at the origin of both of the internal carotid arteries (Figure 8). On neurologic examination the patient was alert but had flaccid hemiparesis on the right side. Carotid arteriograms were repeated and a shift in the anterior cerebral artery and depression of the middle cerebral artery, consistent with a left frontoparietal tumor, were noted (Figure 8). Craniotomy was performed a month after admission and an inoperable glioblastoma multiforme was found. The patient became progressively worse and died a month later.

Discussion. During previous examination of this patient, lesions at the origin of both internal carotid arteries were found. Because of the progression of symptoms and inadequate intracranial visualization in cerebral arteriograms taken before referral, a second arteriogram was taken which showed an unequivocal space-occupying lesion.

Atherosclerotic lesions of cerebral vessels are common and cerebrovascular occlusive disease may be found in patients whose symptoms are due to other lesions. Despite expert neurologic consultation, approximately 2 per cent of the patients in our series eventually were found to have brain tumors. In one instance, vascular reconstruction was actually done before the tumor was recognized. Satisfactory cerebral arteriograms which permit good intracranial visualization are of great value in detecting unsuspected disease. One must be constantly alert to the fact that lesions other than arteriosclerosis may be present. If the pathologic findings do not correlate with the symptoms, critical reassessment of the patient is required.

Discussion

Until recently, stroke was thought to be caused by occlusion of small arteries supplying the ischemic area of the brain.[7] In the present series, evidence of atheroma was rarely found in these smaller arteries. Careful clinical evaluation can localize the symptomatic area of the brain and the area of maximum ischemia, but locating the specific artery or arteries responsible for the patient's symptoms is much more difficult. The case reports illustrate the variety of clinical symptoms found in cerebrovascular disease as well as the variability of the findings and the frequency of multiple vessel involvement. Case 1 was a typical example of the far advanced stage that arteriosclerotic disease can reach without major localizing symptoms. In similar circumstances, an ischemic focus could occur anywhere in the brain, depending upon the relative adequacy of collateral vessels to any one area.

Even when the occlusion is within the intracranial vessels, the source of the disease is frequently the larger proximal vessels.[6] In Case 2 the significant lesion was the relatively unobtrusive plaque in the carotid artery in the neck. The stroke in this case resulted from slough of an atherosclerotic plaque with embolic occlusion of the middle cerebral artery.

Cerebral angiography may not always be successful in locating the lesion responsible for stroke. These lesions may disappear without a trace within days or weeks following the acute occlusive episode. Case 3 was an excellent example of a major stroke caused by occlusion of the internal carotid artery but which follow-up arteriography showed to have resolved completely. Smaller fibrin emboli may also cause transient ischemic attacks. Objective evidence for the presence of the lesions is the observation of fibrin emboli in the retinal arteries which disappear on serial observation.[4]

Arteriography may reveal pathologic changes other than atherosclerosis as the cause of symptoms. In Case 5, the heart was found to be the source of the embolus. However, cerebral arteriosclerosis is common, and under normal circumstances lesions may produce symptoms as a result of hemodynamic changes due to changes in posture, blood pressure or cardiac output.[2,8] In addition, one must be on his guard lest symptoms caused by brain tumor, aneurysm or other vascular malformations be attributed to atherosclerosis after incomplete visualization of the intracranial vasculature.

These cases indicate how therapy can be much more specific and effectively directed if the nature of the pathologic process is verified. When a lesion is apparently the result of hemorrhage under an atherosclerotic plaque, treatment with anticoagulants would be ineffective, nor would such agents aid in treatment of smooth stenotic lesions or of lesions that are complete and stable. Obviously, anticoagulant therapy would be indicated for embolic lesions and surgical therapy for brain tumors, aneurysms and certain extracranial occlusive lesions.

In spite of the advantages of precise diagnosis obtainable with cerebral angiography, the disadvantages—morbidity and mortality—must be considered. In light of the serious implications of stroke the minor hazards that are entailed, the discomfort and the cost of the procedure are all acceptable burdens.[11] All the arteriograms in this series were done by surgical residents in the second, third, or fourth year of training. They were responsible for all angiography performed on an active vascular service over a four-month period. This experience is probably typical of any well-equipped, well-staffed hospital which does these procedures frequently. If responsibility for the examination lay regularly and permanently with one or two experienced persons, the risk of the procedure would probably be even less. However, when the serious implications of the disease are considered, the mortality rate of 0.67 per cent and the major neurologic complication rate of 2.3 per cent are quite low. During the period of this study, a similar number of patients in whom angiography was not performed had major neurologic complications or death from stroke. In addition, the indirect benefits of angiography in the diagnosis of unsuspected lesions such as brain tumors, aneurysms and cardiac emboli alone seem to outweigh the risk. Angiography permits a clearer, more concise understanding of the cause of stroke, permits the intelligent application of therapy and can be accomplished with little risk to the patient.

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GENETIC COUNSELING

A Health Department Service to Physicians

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■ *Questions about inheritance in all kinds of diseases and defects are commonly asked of nearly all physicians. In attempting to answer these questions, however, the physician is often hampered by lack of formal instruction in clinical genetics.*

Since the health department, if it is to carry out its epidemiologic function, must be as concerned over the increasing identification of genetic agents in disease as it is and has been over environmental disease agents, it should come to represent a source of assistance not now generally available to the physician. In short, as it carries out those activities by which its store of general genetic information is increased, and until other sources of genetic consultation become reasonably available, the health department can be of real service to physicians as a resource to which they may turn for help when dealing with families wanting genetic information.

Such a service has been provided experimentally for the last two years by the Contra Costa County Health Department.

This program calls for the taking of family pedigrees by public health nurses on families with questions of a genetic nature who are health department clients and on families who are referred by their private physicians for this service. An interpretation of each pedigree is made by the department's physician in charge of the program and submitted to the family's physician for his use in counseling the family. Evidence to date suggests the process can be a highly useful service to the practitioner and his patient.

BECAUSE THE TERM "genetic counseling" has been so variously interpreted, any discussion of the role or the potential role of the private practitioner in this area must begin with a clear understanding of the meaning of terms.

Genetic counseling is considered here to be simply the communication to an affected family or individual of any genetic information about a given disease. The physician who tells his patient that the disorder in question tends to "run in families" is alerting the patient to the possibility of an increased risk to others in the family; and under the above definition he is providing genetic counseling just as surely as the hospital-centered medical geneticist who communicates a fuller report of risks, based on a comprehensive study of the

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entire family. While the counselor's own knowledge will determine how much of what kinds of information can be given, optimum counseling will include as much of the following as is known to the counselor: how the disease (or predisposition) is inherited, who else in the family is at risk, how much of a risk this appears to be, whether or not it is possible to detect genetic carriers or potential cases from among these high risk persons, how symptoms might be prevented or postponed in those who are so detected, and what services exist in the community for each course of action the family may decide to pursue.

Acceptable genetic counseling allows the individual to arrive at his own decisions without persuasion in any personal issues that arise (for example, marriage, procreation).

The Genetic Counselor

The ideal genetic counselor, being an expert in many different disciplines at once, exists only as a concept. In practice, counselors are usually expert in only one or two fields, most counseling being done by either geneticists or physicians. The geneticist has the advantage of his genetic knowledge in interpreting hereditary factors and how they operate. The physician has the advantage of his knowledge of the medical implications, of his more intimate relationship with the family, and of the position he is in to follow through with what seems indicated medically. Most questions concerning heredity do not require of the counselor an advanced degree in genetics and most genetic information that is being given is not being given by geneticists. Simple questions by patients or comments about heritability by patient are a several-times-a-day occurrence in many physicians' offices, and physician responses to these questions undoubtedly make up the vast bulk of what genetic counseling is going on in any community whether the physician labels it as genetic counseling or not and whether or not his answers are as complete or even as accurate as they might be.

That people do and will continue to turn primarily to physicians for genetic information is to be expected, since one's heredity becomes a motivating concern usually only where a disease or defect is involved. Nor can the physician comfortably ignore such requests since his concern with disease requires that he also be concerned with its cause and therefore with whatever hereditary influences are involved.

In effect, then, the private practitioner emerges as the usual source of genetic counseling in the community, with or without access (usually without) to any of the few existing genetic counseling centers to which he might refer his knottier problems. Because the volume of requests he and his colleagues get for genetic information could not be handled by any one center (even if there were enough centers and geneticists) and because most requests actually do not call for the all-out efforts of a center, the private practitioner is likely always to be in the position of having to tackle the majority of such requests by himself—which implies, of course, that he must also be able to discern that minority of cases that do call for outside help.

Counseling by Private Practitioners

While there seems to be little doubt that most genetic counseling is done by physicians, that most physicians do genetic counseling, and that they may be considered for more than one reason to be the logical source for most of this kind of information, even so the average physician has some real question about his own performance in this area. Rarely in his previous training has he been given any formal instruction in clinical genetics that would make his job easier and that would make him more comfortable doing it.

The same can be said of health departments, where the impact of genetic factors on community health can no more be ignored than their impact on the health of the individual. Genetically influenced disabilities make up the bulk of Crippled Children's caseloads. The majority of disorders with which chronic disease programs are concerned are demonstrably influenced by heredity. Epidemiologic study and centralized informational services, both of which the public health agency has traditionally carried out with respect to environmental agents in disease production, now need to be as industriously carried out with respect to genetic agents. Like the individual practitioner, the health department is hampered by a lack of orientation in this field. It must shortly set about the business of procuring or developing the expertness it needs; and when it does, it is going to have to decide what, beyond carrying out its epidemiologic and other research functions, it ought to be providing in the way of service.

It is our proposal that such agency services, if they are to take the most useful and practical form possible, and if they are going to be available to the entire community, must consist of measures specifically designed to support or aid the private physician in his current role as the genetic counseling resource for the bulk of families in the community—whether this be done by providing genetic information or consultation to physicians wanting it, by stimulating the development of expert genetic counseling and research centers, by encouraging medical specialists into this field to serve as resources to their fellow practitioners, or even by promoting (and educating on the need for) an increasing integration of clinical genetics in medical school curriculum.

It was in this belief that the Contra Costa County Health Department two years ago began a direct information and consultation service to physicians. While it is still too early to evaluate certain aspects of the program, the evidence to date is encouraging enough to merit describing the program here as an example of the kind of assistance the private practitioner might come to ask of his public health agency.

Contra Costa Program

Thus far the program has been conducted on a demonstration basis for the purposes of evaluating the service itself and of acquainting practicing physicians with what it is and what it offers. Although it has involved chiefly families who are health department clients wanting to know more about the heritability of congenital or chronic health problems that affect them, the service is available to any Contra Costa family at the request of the family's physician.

Its purpose is to provide the physician with genetic information that may be useful to him in counseling the patient with a hereditarily influenced disorder. It does not necessarily attempt to provide all the answers in all cases, nor does it provide diagnostic investigation of families. It is intended simply to assist the physician in handling a greater proportion of the genetic questions and problems which face him and to help as well in identifying those situations that cannot be handled without outside help or special investigation.

In each case the first step in the process is the compilation of a family pedigree. This is done by public health nurses, all of whom have been oriented in the technique. All pedigrees are obtained at home visit. If the nurse has had no previous contact with the family, as is often the case with families who are privately referred for this service, the referring physician is asked to inform the family beforehand of the nurse's visit and its purpose.

In composing the family pedigree, the nurse asks the family informants about the health status of each relative so that all health problems are included in the pedigree. As a minimum the following living and dead family members are included: the principal—that is, the person seeking information—his siblings, his parents, his aunts and uncles and their offspring, his grandparents, plus every additional relative known to have had whatever disorders may have been had by any of these main relatives.

Pedigrees are than submitted to the health department physician responsible for the program for an interpretation as to what the pedigree itself suggests and what information is available in the literature. Since the interpretation is meant to serve as a basis for genetic counseling, it includes as much of the information described earlier regarding risks and potential susceptibles as is available or apparent to the interpreter.

A copy of the pedigree and the interpretation are then sent to the family's physician for his use in counseling the family—that is, to the referring physician in the case of private referrals, or, in the case of health department clients wanting genetic information, to their usual source of medical care, whether private or clinic. Along with this material goes a cover letter explaining the purpose for which it is intended.

The health department physician responsible for the program is available to counsel families directly but does so only where the family requesting information has no source of medical care or, in the case of private referrals, where the referring physician requests it. In actual practice, all physicians who have thus far referred families for genetic study have provided their own counseling on receipt of the pedigree and its interpretation.

A copy of the interpretation is also sent to the nurse who obtained the pedigree so that she will be able as needed to reinforce the physician's counsel. All referring physicians are informed of the availability of this service should they wish to use it.

Thus far, over 300 families with a wide variety of congenital and chronic disorders have been studied. In 35 per cent of cases, the mode of genetic transmission of the disorder has been clear cut enough to allow a precise prediction of the risks to other relatives and future offspring. This group includes, for example, cystic fibrosis, muscular dystrophy, phenylketonuria, primary glaucoma, polycystic kidney, polydactyly and congenital spherocytosis. Another 59 per cent of families has represented conditions in which the mode of inheritance of the given disorder, or of the predisposition to that disorder, is not yet fully understood but for which at least some genetic information is available that might be considered useful by the physician or the family (for example, diabetes, rheumatic fever, thyroid disease and cleft lip).

To date most of the families studied have been health department clients, and the majority of private referrals have come from physicians who have already received this service around some family from the former group.

Seventy-four physicians have been sent interpreted pedigree material. While it is still too soon to ascertain what the general response of physicians is, we have received enough spontaneous expression of physician satisfaction with the material and, in the case of health department clients, of family satisfaction with the information they have subsequently received to feel the program has a real potential for service to the practitioner and the families he serves.

Prospectus

While it may still be too early to prophesy the ultimate outcome of this kind of public health effort, several developments seem likely. If the pedigree approach proves to be a useful tool to the practicing physician, the eventual development of an easily followed format which would enable the family to compile its own pedigree can be anticipated as a necessary time-saver for both physician and public health nurse. One might also anticipate an increase in health department services of the informational or clearing-house type abetted by increased epidemiologic efforts in the area of population genetics.

The emergence of medical genetic specialists within the community seems another likely possibility as physicians with a special interest in genetics are encouraged into this field to serve as resource consultants to the other practicing physicians in the area.

Lastly, the beginning integration of clinical genetics into medical school curriculum cannot help but be measurably facilitated by the active incorporation of the genetic approach into the ongoing practice of medicine in the community at large.

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Acute Rheumatic Fever
In Los Angeles County

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■ *There was a general downward trend in the reported incidence of acute rheumatic fever in Los Angeles County during the years 1954-1963. A survey of hospital records in five large hospitals in 1962 revealed 100 cases diagnosed, 39 of which were reported. Diagnoses in the charts reviewed conformed to the Modified Jones Criteria. Most of the patients were born in Los Angeles County.*

Mortality rates for acute rheumatic fever during the same period were greatly in excess of those expected from the reported morbidity. The mean crude mortality rate for the period concerned was higher than for New York City, although not as high as for Boston.

Acute rheumatic fever appears to constitute a health problem in need of review in Los Angeles County.

THERE IS NOT MUCH INTEREST among medical groups in Los Angeles County in the promotion of community programs dealing with the prevention of acute rheumatic fever. Apparently this is because the disease is considered only a minor health problem hereabouts. Since it appears to be the basis for a generally held opinion, the magnitude of the problem in the Los Angeles community seemed worth determining. Hence the present study.

Reporting

Health Departments. The California State Department of Public Health lists acute rheumatic fever as a reportable disease.[1] As shown in Chart 1, during the last ten years there was a general downward trend in the reported incidence of acute rheumatic fever in Los Angeles County, while the reported streptococcal infections remained of a constant magnitude.

With rare exceptions—for example, smallpox and poliomyelitis—reportable diseases are not completely reported. It can be assumed, then, that not all cases of acute rheumatic fever are reported. But what proportion is reported?

Hospital Records. Records of cases for the year 1962 (the last year for which full records were available) in which the discharge diagnosis was acute rheumatic fever were reviewed in five of the largest general hospitals in Los Angeles County. In addition, medical records librarians of 15 hospitals with over 200 beds were asked the number of patients discharged with that diagnosis in that year.

There were 100 cases diagnosed in the 20 hospitals during the year. The total number of cases

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Submitted November 6, 1964.

reported in the County during the same period was 39.

Of 33 charts in the five largest hospitals, 13 were for patients resident in the city of Los Angeles. Six of these 13 within the jurisdiction of the city health department were reported.

Patient Characteristics, Disease Manifestations and Treatment

Twenty-eight of the 33 charts at the five largest hospitals were reviewed. The following comments apply only to the group of charts reviewed. As indicated in Tables 1, 2, 3, and 4, distributions for age and sex and manifestations seemed to follow ordinary patterns.[7] Distribution for race seemed consonant with the populations served by the hospitals concerned. In general, treatment followed accepted recommendations for eradication and prophylaxis of beta hemolytic streptococcus. The use of steroid therapy was not statistically related to the presence or absence of carditis.

TABLE 1.—*Age and Sex, 28 Patients with Acute Rheumatic Fever*

	0 to 9	*10 to 19*	*20 to 29*	*30 to 39*	*40 to 49*	*50 to 59*	*Total*
Male	2	6	1	1	1	....	11
Female	6	8	2	....	....	1	17
Total	8	14	3	1	1	1	28

TABLE 2.—*Age and Race, 28 Patients with Acute Rheumatic Fever*

	0 to 9	*10 to 19*	*20 to 29*	*30 to 39*	*40 to 49*	*50 to 59*	*Total*
Negro	4	6	....	....	....	....	10
White	4	8	2	1	1	1	17
Unknown	....	....	1	....	....	....	1
Total	8	14	3	1	1	1	28

TABLE 3.—*Age and Place of Birth, 28 Patients with Acute Rheumatic Fever*

	0 to 9	*10 to 19*	*20 to 29*	*30 to 39*	*40 to 49*	*50 to 59*	*Total*
Calif.—L.A. County	3	5	....	....	....	....	8
Calif.—L.A. County or elsewhere	2	3	....	....	....	....	5
Outside California	2	5	1	....	1	1	10
Unknown	1	1	2	1	....	....	5
Total	8	14	3	1	1	1	28

TABLE 4.—*Data on Manifestations of Disease and on Treatment Reported in 28 Cases of Acute Rheumatic Fever*

	Nature of Treatment								
	Steroid	*No Steroid*	*ASA**	*No ASA**	*Penicillin Received*	*No Penicillin Received*	*Prophylaxis*	*No Prophylaxis*	*Unknown*
Carditis	7	10	11	6	13	4	12	3	2
No Carditis	2	9	10	1	9	2	10	....	1
Total	9	19	21	7	22	6	22	3	3

*Acetylsalicylic acid.

Morbidity and Mortality

Figures for deaths in Los Angeles County during the nine-year period 1954-1962 which were coded as due to acute rheumatic fever (ISC 400-402) are shown in Table 5. If one accepts the supposition that not more than one in twenty cases of acute rheumatic fever should be fatal, the case fatality rate is 5 per cent or less. If expected morbidity is computed from mortality using this rate, approximately ten times as many cases are occurring as are reported. If the case fatality rate is lower, such as the 1.2 per cent found in the Co-operative Rheumatic Fever Study of 1955, then even more cases are occurring.[3] If one assumes, on the other hand, that some of the deaths were miscoded, then the expected morbidity on the table should be decreased. Twelve of the 21 patients reported as having died of rheumatic heart disease in 1961 were residents of Los Angeles City. Dr. Herbert Cowper, Director, Division of Communicable Diseases, reviewed the 12 death certificates with the attending physician and found that in five cases death was not due to acute rheumatic fever.[4] Whether these 12 cases are representative of the 196 deaths recorded for the period is not known.

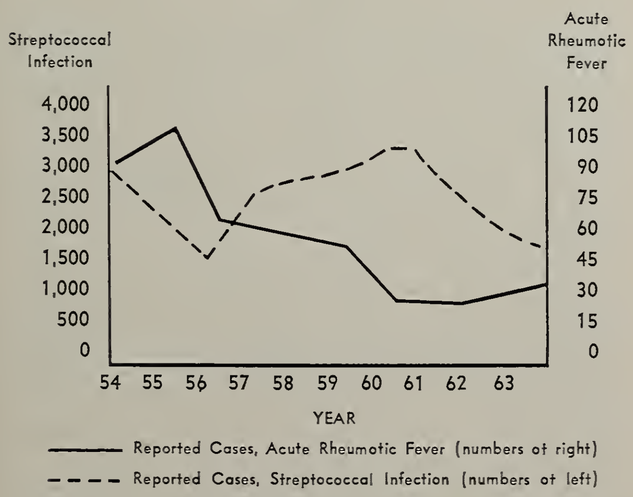

Chart 1.—Streptococcal and acute rheumatic fever reporting, Los Angeles County, 1954-1963.

The accuracy of the diagnosis listed on the death certificates in Los Angeles County, however, is probably comparable to that in other areas.

TABLE 5.—*Acute Rheumatic Fever Morbidity and Mortality, Los Angeles County, 1954-1963*

Year	*Deaths*	*Expected Morbidity*[1]	*Cases Reported*
Total	196	3,920	617
1954	31	620	99
1955	29	580	110
1956	23	460	74
1957	19	380	68
1958	19	380	63
1959	17	340	58
1960	22	440	35
1961	21	420	32
1962	15	300	39
1963	[2]	[2]	39

[1] Assuming a 5 per cent case fatality rate. [2] Not available.

TABLE 6.—*Acute Rheumatic Fever Deaths in Los Angeles County Compared with Other Areas, 1954-1962*

Year	*L. A. Co.*	*Dade Co., Fla.*	*New York*	*Boston*
Total deaths	196	29	240	52
1954	31	3	61	7
1955	29	3	30	7
1956	23	4	29	1
1957	19	3	29	7
1957	19	7	20	10
1959	17	6	20	5
1960	22	1	26	1
1961	21	0	8	10
1962	15	2	17	4
Mean	22	3.2	27	5.8
	5,680,000	853,000	7,810,000	725,000
Mean per 100,000	0.39	0.38	0.35	0.80

Comparison With Other Areas

Northern cities are supposed to have higher incidence of rheumatic fever than southern cities. It is of interest therefore to note (Table 6) that the mean crude mortality rate for acute rheumatic fever in Los Angeles County is higher than that for New York City, although not as high as for Boston. Interesting also are the equal mortality rates in New York City in the north and Dade County, Florida, in the south. Housing and socioeconomic levels are also factors in the incidence of this disease.

Comment

This report is a collection of data gathered from various hospitals, local health departments and a state health department. Although crude and not definitive, they indicate that acute rheumatic fever may have a higher incidence in Southern California than is currently believed. Indeed, the mean mortality rate in Los Angeles County is greater than in New York City although less than in Boston. Both eastern areas have extensive facilities and programs for diagnosis and treatment, as well as follow-up for secondary prophylaxis, which is of vital importance to good rheumatic fever care.

In a recent article from Chicago, Siegal[8] noted that 700 new cases of rheumatic fever were reported in that city in 1962 and 668 in 1963. La Rabida Sanitarium renders care to a significant proportion of children in the Chicago area requiring care in hospital for acute rheumatic fever; and during 1960-1961, 110 patients with first attacks of acute rheumatic fever were admitted to that institution.[6]

Not so many years ago Chavez[7] indicated that acute rheumatic fever was not uncommon in Mexico, and there is a great deal in that country today.[5] Ultan and Goodman[9] recently noted a gradual increase in *reported* cases in Puerto Rico following initiation of educational and preventive programs. Since the climates of these areas are not too different from that in Southern California, it would not be inconsistent to expect a significant incidence of acute rheumatic fever here. The problems of evaluating incidence data are many, and they are thoroughly discussed by Paul.[7]

It is not the purpose of this article to imply that acute rheumatic fever is the most important disease of younger people in Los Angeles County or that it is the most prevalent cardiovascular disease in this locale. From the data presented, however, acute rheumatic fever would appear to constitute a greater health problem than is generally believed. The epidemiology, primary prevention, clinical diagnosis and treatment and secondary prophylaxis of acute rheumatic fever deserve attention and study in this community.

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STUTTERING

The Effect of Treatment with D-Amphetamine and a Tranquilizing Agent, Trifluoperazine

A Preliminary Report on an Uncontrolled Study

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■ *In an institution for the mentally retarded, an uncontrolled study was made on the effects of d-amphetamine, d-amphetamine followed by trifluoperazine, and of combined d-amphetamine and trifluoperazine on stuttering. Of 28 patients to whom d-amphetamine was given, 14 showed improvement after one month's treatment. Eight more showed improvement when trifluoperazine was given for one month to those who did not improve on d-amphetamine. In many cases, improvement was sustained at least six months after treatment was discontinued.*

Treatment with d-amphetamine was apparently more effective in patients with functional than with organic retardation.

IN RECENT YEARS a variety of psychopharmacologic agents have been increasingly used in the control or treatment of functional disorders. In 1953, Ginn,[3] using d-amphetamine in treatment of behavior disorders in children, noted improvement in the speech of two of four stutterers. The senior author of the present study, who stuttered, noted decided improvement in speech while taking d-amphetamine for obesity in 1957. An exploratory study done by him in 1957 on five adult male patients indicated that d-amphetamine improves speech in stutterers and that controlled studies were merited. In 1961, Fish and Bowling,[2] in a double blind study, observed that five of eleven stutterers showed improvement in speech. None of the other speech defects of patients in that study were improved significantly by d-amphetamine. Continuing administration of d-amphetamine for three months did not bring about improvement in the six stutterers who were not benefited earlier.

It was suggested that perhaps those stutterers who do not improve on d-amphetamine, which is a psychic and muscular stimulant, might improve on a tranquilizer. Perusal of the literature[1,4,5,6] indicated that tranquilizers apparently do not improve speech in stutterers. However, it was felt that selection of patients who did not improve on d-amphetamine might be worth a trial with a tranquilizer.

Materials and Methods

At Fairview State Hospital, an institution for the mentally retarded, there were 34 stutterers

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Fairview State Hospital, Costa Mesa.
Submitted May 13, 1965.

whose degree of stuttering had recently been evaluated. The criterion for evaluation was a practical one: the extent to which stuttering interfered with verbal communication. Three categories, severe, moderate and mild, were used. The patients ranged in age from 10 to 59 and in intelligence quotient from 21 to 77. There were five females and 29 males. Of these 34 patients, six who were not available to receive medication on the day the study was begun, October 1, 1962, were used as controls. The other 28 were given a one-month treatment with d-amphetamine spansule, 15 mg each morning. All other medication such as anticonvulsants and antibiotics, as well as all the scheduled activities, were continued as previously. A one-month trial period was chosen because previous studies showed that most of the improvement, if it occurred at all, came within one month.

Those patients who did not improve on d-amphetamine after one month were given trifluoperazine (Stelazine®) 2 mg three times a day for one month. Treatment was discontinued on all those who improved. Those who did not improve on trifluoperazine were then given a one-month treatment with combined d-amphetamine and trifluoperazine in the same dosage.

The results were as follows:

			Results			
Drug	*Degree of Stuttering*	*No.*	*Improved To*		*Not Improved*	*Worse*
d-amphetamine	Severe	8	Moderate or Mild	3	5	0
	Moderate	10	Mild	6	3	1
	Mild	10	None	5	4	1
	Total	28		14	12	2
Trifluoperazine	Severe	6	Moderate or Mild	4	2	
	Moderate	4	Mild	3	1	
	Mild	2	None	1	1	
	Total	12		8	4	0
	Not available	2				
		14				
Combined d-amphetamine and trifluoperazine	Severe	2			2	
	Moderate	1			1	
	Total	3		0	3	0
	Not available	1				
		4				

All patients who were still available were reevaluated in January 1963, after all treatment was discontinued (three months after the start of the treatment program) and again in July 1963, to determine if improvement was sustained after cessation of treatment. The results of these reevaluations were as follows:

	Status of Improvement			
	January 1963		*July 1963*	
	Sustained	*Not Sustained*	*Sustained*	*Not Sustained*
Patients who improved on:				
d-amphetamine	6	3	5	3
trifluoperazine	4	2	2	3
Total	10	5	7	6
Five controls	No change		No change	

The per cent of sustained improvements might possibly have been higher if those not available for reevaluation could have been tested, since most of them had left the hospital because of general improvements in their condition.

In order to determine if differences in the kind of mental retardation might be a factor in the differing responses of the stutterers to d-amphetamine or to trifluoperazine, two broad categories of causes of mental retardation were used, *organic* (congenital malformations, brain injuries due to disease or trauma, anoxemia at birth, inborn errors of metabolism and the like) and *functional* (mental retardation with no known anatomical or metabolic cause, or retardation owing to emotional disturbance or psychosis). The numbers of patients in each category and the numbers in each who were improved by two methods of treatment were as follows:

	Organic		*Functional*	
	Improved	*Not Improved*	*Improved*	*Not Improved*
d-amphetamine	3	7	11	7
trifluoperazine	5	2	3	2

Proportionally, the results with d-amphetamine were better in the functional than in the organic group. With trifluoperazine, the converse was true.

Discussion

The present study corroborates previous studies in that approximately 50 per cent of stutterers improved on a d-amphetamine regimen, and a considerable proportion sustained this improvement for at least six months after cessation of treatment.

A total of 22 out of 26 available patients showed improvement on one or another of the regimens. The five control patients who were reevaluated showed no change in their stuttering during this total period. The question arises whether the improvement on trifluoperazine was due to the tranquilizer *per se* or may have owed something to the previous "priming" with d-amphetamine. Or possibly there are two types of stutterers, one affected by d-amphetamine and the other affected by trifluoperazine. In view of previous negative reports of the effects of tranquilizers alone on stuttering, the latter two possibilities should be further investigated.

The mechanism of action of d-amphetamine on stuttering is not known. It is possible that d-amphetamine with its psycho-stimulating properties produces a sense of well-being, thereby reducing fear and anxiety and thus breaking the habit pattern: stuttering, causing fear and anxiety, causing more stuttering. That this mechanism is the more plausible is suggested by two observations: (1) Stuttering on a functional basis or in the functionally mentally retarded is improved by d-amphetamine more often than stuttering associated with organic mental retardation; and (2) the improvement is sustained in many cases long after cessation of treatment. There is also the possibility that the patients with organic mental retardation who improved had a functional overlay as a cause of stuttering. Another mechanism of action that has been suggested is that stutterers, having a response-weakness in their muscles of speech, respond to a priming of the skeletal muscular system by a muscle stimulant, similar to the response of symptoms of myasthenia gravis to ephedrine or neostigmine.

Further studies that appear to be in order are:

1. A controlled double blind study with d-amphetamine on stutterers with normal intelligence.
2. A study with a "psychic energizer" which is not a muscle stimulant.
3. A study with a muscle stimulant which is not a "psychic energizer."
4. A controlled double blind study with d-amphetamine followed by trifluoperazine, as opposed to trifluoperazine followed by d-amphetamine.
5. Use of tablet form of d-amphetamine instead of time-release spansules (personal communication from a physician who has used both, indicates that there is more improvement with the tablet form).
6. Intermittent use of d-amphetamine, one month in every three months for one or more years, as opposed to use of d-amphetamine for one month followed by speech therapy for a similar period.
7. Evaluation by speech therapists of changes in the whole stuttering syndrome, rather than just changes in verbal stuttering, before and after one month's therapy with d-amphetamine.

The authors are carrying out studies proposed in Items 1 and 7 in the above list and plan to do others as circumstances permit. However, reports by others doing similar studies would be most welcome.

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Pollen and Mold Spores

An Atmospheric and Field Survey in Los Angeles

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■ *A two-year survey of pollen and mold spores by the gravity slide method revealed that there are no clear-cut tree, grass or weed pollen seasons in California.*

Pollen counts should be correlated with field studies to distinguish the various plants whose pollen have a similar appearance.

Spores of Alternaria *and* Hormodendrum, *whose importance in allergic disease of the respiratory tract has been well established for many years, were found all during the year. More* hormodendrum *spores were collected than the total of all other pollens combined.*

IN COMMENTING on the cause of hay fever, Elliotson[3] in 1831 stated that the affliction "certainly . . . does not depend upon the hay . . . but upon the flower of the grass, and probably upon the pollen."

Forty years elapsed before Blackley[1] gave conclusive experimental proof that grass pollen is the cause of "summer catarrh." He observed that these pollens, when injected subcutaneously, produced a reaction similar to that of the common scratch test. Blackley was the first to take a pollen count by means of coated glass slides. He even sent them aloft on kites to determine the pollen dispersal at various altitudes.

Since that time, allergists all over the world have been making "routine" pollen counts. They have devised various methods to check the accuracy of these counts, and to evaluate them in terms of their clinical significance. Small[7] combined pollen counts with botanical surveys, he even mounted slides on his car to check the atmosphere pollen in various areas of Southern California.

Several years ago one of us[6] did a field survey of giant ragweed (*Ambrosia trifida*) in Iowa City, Iowa, finding 146 acres of ragweed growing in a city with a total area of 3,315 acres. During the subsequent fall pollen season, 10 sampling sites were selected to determine the local dispersal of ragweed pollen. Standard samplers were placed six feet above the ground and pollen counts on them were compared with those from a centrally located sampler 75 feet above the ground. It was found that the samples obtained at the centrally located site were representative of the pollen counts at ground level.

Materials and Methods

The present study covered a period of a little over two years beginning in August 1962, and ending in September 1964. The standard technique for atmospheric pollen sampling by the gravity slide method was used. It is approved by the American Academy of Allergy, and has been used in reporting pollen studies since 1946.[2]

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Microscopic slides coated with a thin film of vaseline were exposed for 24 hours in a standard gravity sampling device. The sampler designed and described by Durham[2] has been in general use for many years.

Slides were exposed daily in Huntington Park, California, from August 1962 through September 1964, and at a second sampling site at the Los Angeles County General Hospital from July through September 1964. At both stations the sampler was located on the roof, free of obstructions to cross-currents of air.

All the pollen grains and mold spores on two square centimeters of slide area were counted without staining. The result is reported in terms of one square centimeter of slide area per 24 hours.

Daily climatological data was available from the weather bureau. The average monthly temperature during the period of this study was 65°F, with a variation of 55° to 77°. Winds were mainly westerly at an average speed of six miles an hour. The average amount of sunshine was 77.5 per cent, with a variation from 52 to 96 per cent. The relative humidity averaged 45, with a range of 24 to 56. The total rainfall during the first year of the study was 8.38 inches and during the second year it was 7.93 inches, compared with a normal yearly total of 14.68 inches.

In conjunction with the pollen counts, we made frequent field surveys to observe the current flora and correlate the observations with pollen counts. This is very helpful in Southern California where there are large numbers of wind-pollinated plants, many of which can only be identified as to families on the basis of their pollen structures.

Chart 1 shows the pollination times of the most important plants whose pollen was found on our slides during this study. The number in parentheses signifies the total yearly count per square centimeter of slide area. A glance at this graph will show that Southern California, unlike other areas of the United States, does not have clear-cut tree, grass or weed seasons. In Southern California we have seen walnut pollen as early as January in some years. The peak incidence occurs in April. The most common species are *Juglans regia,* an English walnut that at one time was widely cultivated in groves, and *J. californica,* which is a native tree. Oak pollen, which also has its peak incidence in April, is the most abundant of all pollens seen on the slides. *Quercus agrifolia* is the most important species of oak in this area.

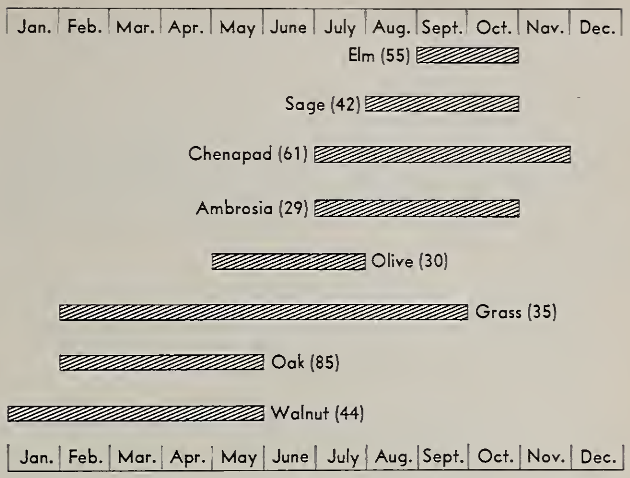

Chart 1. Pollination times and yearly total of pollens per square centimeter of slide area. Data collected from August 1962 through September 1964.

Olea europa or olive, the other important spring tree pollen, has a peak incidence of pollen in May. Sycamore pollen is found frequently but is of less importance clinically.

Grass pollen was found on the slides from February through September. The counts were low, however, as has been reported in most pollen surveys in California and in other areas of the United States. Nevertheless, the large number of people who have positive skin test reactions and the frequent clinical correlations, leave no doubt as to the importance of grass pollens. The following is a list of grasses which were most commonly found on our field trips:

1. Spring grasses—
   a. *Cynodon dactylon*—bermuda
   b. *Avena fatua*—wild oats
   c. *Bromus rigidus*—broncho grass
   d. *Lolium perenne* and *L. multiflorum*—English and Italian rye grass
   e. *Poa annua* and *P. pratensis*—annual Kentucky blue grass.
2. Late spring and fall grasses—
   a. *Cynodon dactylon*
   b. *Poa annua*
   c. *Holcus halepensis*—Johnson grass

Bermuda is the most common grass. It is seen all during the spring, summer and early fall. Johnson grass is commonly seen in large stands as late as December.

Many other species of grasses were found but they are less abundant, produce insignificant amounts of pollen or are not thought to be important clinically.

Pollens of the family *Chenopodiaceae* are found as early as January but do not occur in large numbers until July. They reach their peak incidence in August and September. Since the pollen grains of many Chenopods are quite similar, one kind to another, our field surveys were very helpful in determining which of these weeds were pollinating. The following is a list of the Chenopods in their approximate order of appearance of pollen from them in the Los Angeles area:

Chenopodium murale—early spring
Chenopodium album (lamb's quarter)—summer
Amaranthus retroflexus (pigweed)—late summer
Solsola kali (Russian thistle)—fall

We again encountered the problem of similarity of pollen structure in the family *Ambrosiaceae,* which includes the following commonly seen weeds:

Ambrosia psilostachya (western ragweed)
Franseria acanthacarpa (false ragweed)
Franseria bipinnatifida (no common name)

Their pollen is seen on the slides from July through October, with the peak in September. However, *A. psilostachya* was seen growing as late as January.

Artemisia, or sage was found from August through October. The most common of the species is *Artemisia californica* or costal sage.

Pollen of *Plantago lanciolata* or English plantain was found in small numbers during the spring and summer. As is commonly found in this area, the pollen counts do not reflect the large numbers of these plants found growing during these months. Perhaps this is because the amount of pollen produced by one plantain weed is much less than that produced by one of *Ambrosia psilostachya* or *Chenopodium album.*

Elm, *Ulmus parvifolia* and *U. pumila,* the Asiatic or Chinese elm, is the last important pollen in Southern California in the calendar year. It produces a lot of pollen in a short time—September and October—and is the cause of much discomfort to the allergic patient. The clinical importance of elm is well supported by positive skin test reactions.

These pollination times, as we have noted, are subject to variation from year to year, depending upon climatic conditions, which we have discussed elsewhere.[6] Since the pollen seasons in Southern California are not clear-cut, probably desensitization the year around would be of most benefit to pollen-sensitive persons living in the area.

Fungus Spores

The importance of atmospheric mold spores in clinical allergy has been well established for many years.[4] Again it was Blackley who, in the course of his investigations into the causes of hay fever, tested the influence of molds. After inhaling spores from penicillium cultures, he felt severe tightness in the chest associated with "bronchial catarrh." In our study, spores of *Hormodendrum* and *Alternaria* were found on slides all during the year. An attempt was made to count the individual spores in all clumps. On the basis of a yearly average, *Hormodendrum* spores were twice as common as *Alternaria,* and were about one and a half times as prevalent as all other pollens combined.

There was no seasonal pattern in the incidence of mold spores, but rather a wide fluctuation from day to day. This was previously reported before by Rooks and Shapiro.[5] At that time, we had the opportunity to study the hourly incidence of these spores, using a volumetric sampler. We found that every day was characterized by abrupt hourly changes in the number of spores.

A comparison of these two spores in terms of a volumetric sampler and a 24-hour gravity slide is interesting. On one occasion, a slide count of 22 *Alternaria* represented 776 spores collected volumetrically, and 22 *Hormodendrum* represented 3,416 collected volumetrically. On another day a slide count of 19 *Alternaria* represented 3,000, and 10 *Hormodendrum* represented 59,700 spores collected volumetrically during the same 24-hour period.

These changing daily ratios indicate that the only interpretation which can be placed on gravity slide spore counts is that they show the two spores were airborne on a given day. They also indicate the extent to which the allergic person is exposed to mold spores all during the year.

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The Deceptive Acid Phosphatases

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■ *Determination of the prostatic acid phosphatase is, theoretically, a specific test for carcinoma of the prostate, but the present laboratory techniques have produced too many false positives and false negatives to be dependable. There may be inhibitors or enzymes that interfere with these tests.*

Until more exact enzymes are discovered, the present acid phosphatases should not be depended upon as a criterion for the type of surgical operation in carcinoma of the prostate, nor, without biopsy, should they be taken as an indication of prostatic malignant disease.

ATTEMPTS TO DIAGNOSE carcinoma of the prostate by enzyme analysis have been anticipated ever since Guttman's[5] article regarding acid phosphatases in 1938. However, the unanticipated finding of elevations of the acid phosphatases in cases of benign prostatic hypertrophy and depression of the acid phosphatase even with wide metastasis from carcinoma of the prostate, raised doubts as to the dependability of that test. Hence, a search was made for more specific fractions of acid phosphatase and Fishman[3] discovered a tartrate-inhibited portion which was supposedly produced only by the prostate. This seemed to be more dependable, theoretically, than the total acid phosphatase (TAP) which was produced not only by the prostate but also by the liver, erythrocytes and blood platelets.

The prostatic acid phosphatase (PAP) was not without its laboratory peculiarities. On the one hand, it was found to be very unstable at 37°C and unmeasurable after a short time at that temperature. On the other hand, Delarey[2] and Fishman[3] found elevations of this fraction ranging from 2 to 18 per cent above ordinary levels, in men with normal prostates. It was these contradictory findings in the literature and our lack of understanding of these enzyme variants that initiated the investigation here reported.

Materials

Measurement of PAP and TAP was made in 100 consecutive patients with prostatic disease. The specimens of blood were obtained two days after prostatic examination. None of the patients examined was wearing a catheter. In addition four patients with normal prostates carried out varying degrees of physical exercise before a blood specimen was obtained.

Methods

Determinations of TAP and PAP were done according to the techniques by Guttman and Guttman[5] and by Fishman and Lerner.[4] Blood specimens were immediately refrigerated and picked up by local laboratories. Each test was run in duplicate, the sample permitting. The diagnosis was determined by pathologic specimens obtained by perineal or transrectal needle or wedge biopsy or in the course of prostatectomy, open or transurethral.

Results

The diagnosis was malignant in 21 of the 100 cases in this series, benign in 79. Six of the 29 patients with malignant disease (Chart 1) had elevated TAP and 10 had elevated PAP. These figures represent the findings when only one sample was

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Submitted January 25, 1965.

obtained. If three samples were obtained (Chart 2) there was an increase in the positive findings to 10 and 12 cases in the TAP and PAP respectively. In two of these patients palpation of the prostate indicated no malignant lesion and the TAP was within normal range but the PAP was elevated and eventually carcinoma was diagnosed. On the other hand, unsuspected carcinoma was not found in any case in which the TAP was elevated and the PAP was not. As to "false positives," 13 of the 79 patients had elevations of TAP and 23 had elevations of PAP.

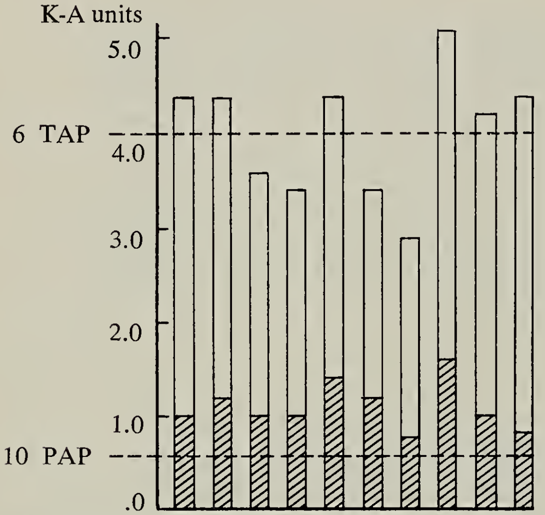

Chart 1.—Six of 21 patients who later were proved to have malignant disease had elevation of total acid phosphatase (TAP) and ten had elevation of prostatic acid phosphatase (PAP) in first specimens tested. White pillars in chart indicate TAP, and those with slanted lines indicate PAP. Dotted lines indicate upper limits of normal, stated in King-Armstrong (K-A) units.

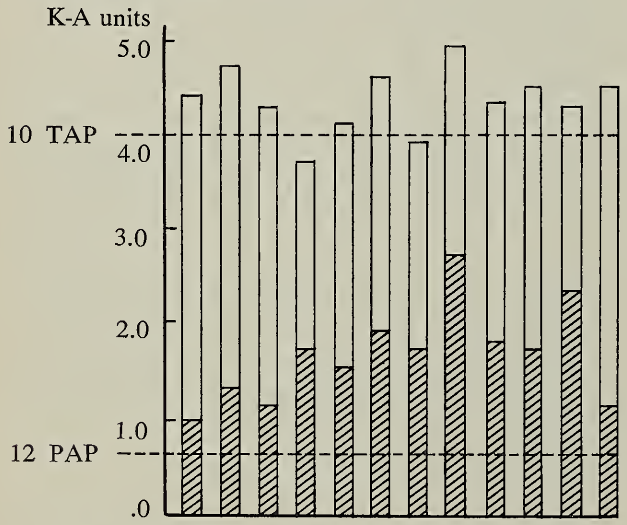

Chart 2.—Ten of 21 patients who later were proved to have malignant disease had elevation of total acid phosphatase (TAP) and 12 had elevation of prostatic acid phosphatase (PAP) in at least one of three specimens. White pillars in chart indicate TAP, and those with slanted lines indicate PAP. Dotted lines indicate upper limits of normal, stated in King-Armstrong (K-A) units.

Discussion

Analysis of the results of this study suggests that the single TAP and PAP tests are not yet dependable in the determination of carcinoma of the prostate with or without metastasis. They become more dependable when more specimens are obtained but with both methods there are too many false positives for accurate evaluation. Possibly, as Amador[1] has suggested, there are inhibitors to account for these errors, similar to those found in the urine for lactic dehydrogenase. Or there may be isozymes of the serum phosphatase similar to the isozymes of lactic dehydrogenase described by Vesell and Bearn.[6] The large number of false positives, especially the PAP in our series and others, has not been explained.

Since most of the patients in this series were ambulatory and had come into the office for examination, it was thought that exercise of varying degrees might force some of the enzyme normally contained within the prostatic capsule out into the general circulation. With this in mind we attempted to determine whether a minimal amount of exercise such as 20 steps of running in place (which we had three patients do) and more strenuous exercise such as running up four flights of stairs (one patient) or walking two miles (the same patient who ran upstairs) would affect the serum acid phosphatase. Specimens were taken before and after exercise. Results varied, with no consistent elevation or depression of either of the enzyme levels in the four patients tested.

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Lung Cancer and Month of Birth

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■ *A statistical study of possible relationship of month of birth to the occurrence of lung cancer was carried out at Veterans Administration Hospital, Long Beach.*

The distribution of the 200 lung cancer cases by month of birth did not differ significantly from that which might be expected by chance alone. These findings do not substantiate those found by Dijkstra in The Netherlands.

IN A REVIEW of 330 cases of bronchogenic carcinoma seen during a 10-year period in The Netherlands, Dijkstra[1] observed that an inordinately large number of the patients had been born during the winter months, with the peak in March. He also noted that a somewhat larger than expected number had been born in the years 1893, 1897, 1898, and 1900.

The Pulmonary Disease Service at the Veterans Administration Hospital in Long Beach, California, cares for a large number of patients with bronchogenic carcinoma. Data on the most recent 200 consecutive patients (all men) with histologically proved bronchogenic carcinoma seen in the year 1963 were analyzed to investigate the relationship between date of birth and the occurrence of lung cancer. The subjects ranged in age from 32 to 80 years with a median of 68.

A control group of 200 patients with pulmonary disease other than cancer was made up at random for purposes of comparison.

The first analysis was concerned with testing

TABLE 1.—*Frequency of two-hundred lung cancer cases at Veterans Administration Hospital, Long Beach, by month of birth*

	Frequency			
Month	*Observed (O)*	*Per Cent Expected*	*Expected (E)*	*Contribution to Chi²**
January	20	7.4	14.8	1.827
February	14	7.8	15.6	.164
March	19	8.7	17.4	.147
April	16	7.8	15.6	.010
May	13	8.2	16.4	.705
June	18	7.7	15.4	.439
July	17	8.8	17.6	.020
August	19	9.2	19.4	.008
September	16	8.5	17.0	.059
October	16	9.1	18.2	.266
November	18	8.2	16.4	.156
December	14	8.4	17.0	.529
Totals	200	99.9%	200.8	4.330

*$\text{Chi}^2_{(.05,\ 11)} = 19.68$.

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the significance of the difference between the distribution of lung cancer cases by month of birth and the distribution to be expected by chance alone. The expected distribution was determined by using the distribution of percentages of total births for each month of 1962 and 1963 as indicated by census data.[2] The chi-square test of significance was used for this analysis. Table 1 presents these data and the results.

It appears that lung cancer is not related to month of birth in the patient population at the Veterans Administration Hospital at Long Beach.

In the second analysis the lung cancer group of patients was compared with the control group, those not having cancer. The chi-square test of independence was used to determine if month of birth is independent of the occurrence or non-occurrence of lung cancer. The data are shown in Table 2.

A chi-square of 8.446 was obtained. This is not significant; therefore, it can be concluded that the occurrence or non-occurrence of lung cancer is independent of month of birth of patients at Veterans Administration Hospital, Long Beach. Nor was there a significant difference when the months were grouped and the analysis performed by season of birth.

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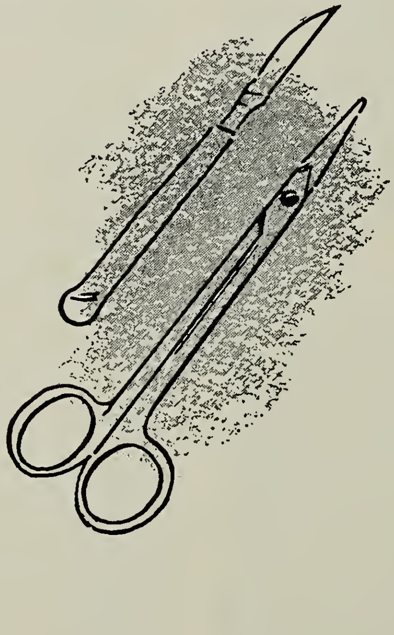
TABLE 2.—*The distribution of 200 lung cancer patients and 200 non-lung cancer patients at Veterans Administration Hospital, Long Beach, according to month of birth*

	Frequency			
Month	*Lung Cancer*	*Control*	*Totals*	*Contribution to Chi^2†*
January	20	20	40	0.000
February	14	17	31	.290
March	19	16	35	.258
April	16	19	35	.258
May	13	15	28	.148
June	18	11	29	1.690
July	17	24	41	1.196
August	19	17	36	.112
September	16	18	34	.118
October	16	17	33	.030
November	18	8	26	3.846
December	14	18	32	.500
Totals	200	200	400	8.446

†$\text{Chi}^2_{(.05,\,11)}=19.68$.



Report of the Committee on SCIENTIFIC INFORMATION

Penicillin Allergy

EDMUND L. KEENEY, M.D.

PENICILLIN hypersensitivity has been classified into the anaphylactic and the serum sickness-like reactions. The anaphylactic reaction appears within minutes after penicillin administration and all the characteristic symptoms of anaphylaxis, including death, may occur. Atopic individuals are most often affected and their sera contains, for a short period, circulating antibodies to penicillin. The serum sickness-like form, which occurs with equal frequency in non-allergic and allergic individuals, is a delayed reaction appearing three to 30 days after penicillin exposure. This is the most frequent adverse reaction, and is unassociated with circulating antibodies to penicillin.

Direct skin tests using benzylpenicillin (penicillin G) as the antigen have not successfully predetermined penicillin allergy because there may be (1) negative tests prior to anaphylactic reactions, and (2) negative tests in individuals having had anaphylactic reactions. Furthermore, severe reactions may occur from the skin test itself.

Recently, immunologic investigation has revealed that some of the degradation products of penicillin exhibit antigenicity and, accordingly, extensive clinical trials with one of these, penicilloylpolylysine as a direct skin testing antigen, have been made. The primary objection to this test is that it gives too many false positive reactions.

There are other diagnostic tests for penicillin hypersensitivity, but they have not been refined sufficiently for general clinical use; these are the serum hemagglutination and basophilic degranulation tests.

Patients suspected of being allergic to penicillin should be treated with an unrelated antibacterial drug. Atopic individuals without a history of penicillin allergy may be given penicillin if there is close medical supervision. When it is mandatory to determine the presence of penicillin allergy, both direct scratch tests with a dilute solution of benzylpenicillin (10,000 units/ml or less), and direct intradermal tests with a dilute solution of penicilloylpolylysine are recommended.

Neither the substitution of penicillin in homologues nor the hyposensitization to penicillin are advised for use in individuals known to be allergic to penicillin.

This statement was prepared by Dr. Keeney, Scripps Clinic and Research Foundation, La Jolla, at the request of the Committee on Scientific Information of the Scientific Board, in response to several queries to the California Medical Association on this subject.

CASE REPORTS

Bilateral Subclavian Steal

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CEREBRAL ISCHEMIA may be produced by reversal of vertebral artery flow secondary to occlusive disease of the first portion of the subclavian artery or innominate artery. The first reports of such cases described involvement of the first portion of the left subclavian artery.[1,9] Mannick[6] later reported a case in which it was the right subclavian artery that was occlusive. Ethier[4] reported the radiographic aspects of a case of bilateral subclavian stenosis in which there was reversal of flow in one vertebral artery and bidirectional flow in the other. Newton and Wylie[8] have presented the radiographic features of a case of occlusive disease of the innominate and the left subclavian arteries. In this case there was reversal of flow in both vertebral arteries and in the right carotid artery. In a review of the literature, no description of the clinical aspects of the bilateral subclavian steal syndrome could be found, nor was there a report of any case in which this syndrome was secondary to bilateral subclavian artery occlusive disease, as it was in the following case.

Report of a Case

The patient, a 49-year-old white woman, had periodic coldness and numbness of the upper extremities, claudication that precluded even such minimal activity as combing her hair, also blurring of vision, vertigo, unsteady gait and nausea. These symptoms had been becoming progressively worse for about a year. At times it was impossible for her to walk through a door or down a hall without staggering into the wall. She had difficulty telling where her feet were without actually looking at them. She also noted decided impairment of memory. The patient lost her train of thought frequently and was unable to recall immediate past experiences easily. During the month before admission to hospital she had repeated occipital headaches that she described as a feeling of pressure. All of the symptoms disappeared when she rested quietly and were made worse by activity. Use of the upper extremities was particularly likely to evoke the symptoms.

On physical examination there was no blood pressure or pulse detectable in either arm. The systolic pressure was 120 in both feet. The carotid pulsations were full and equal. Bruits were heard in both common carotid bifurcations and over the left subclavian artery. Subclavian artery pulsations were not palpable. Both hands and forearms were cool although the skin nutrition appeared unimpaired. The hemogram, results of urinalysis, the fasting blood sugar and the creatinine content were all within normal limits. The VDRL test for syphilis was non-reactive. The serum cholesterol was 350 mg per 100 ml. An electrocardiogram was within normal limits. In a roentgen study of the aortic arch (Figure 1), stenosis of the first portion of the left subclavian artery and complete occlusion of the first portion of the right subclavian artery at its origin were observed. Narrowing was also noted at both common carotid bifurcations. Collateral blood flow to the subclavian vessels was primarily by bilateral retrograde vertebral artery flow. In addition, collateral flow to the left internal mammary artery was demonstrated. Some filling of the branches of the thyro-cervical trunk was also noted.

Submitted 8 July 1965.

A transthoracic left subclavian endarterectomy was performed to remove a long segment of almost totally occluding atheroma extending from the aortic arch to within a centimeter of the origin of the vertebral artery. After this procedure the blood pressure was 130/70 mm of mercury in the left arm and 40/0 mm of mercury in the right arm. All the symptoms were improved. However, as there was still claudication in the right arm and occasional blurring of vision and a mild occipital headache, a right innominate and subclavian endarterectomy was performed 11 days after the first operation. A cervical approach was used, with clavicular resection and division of the right internal jugular vein. The vertebral artery in this particular case arose within 0.5 cm of the origin of the subclavian artery. Hypercarbic fluothane was used for anesthesia. After the operation the patient had normal and equal blood pressure in both upper extremities. She became asymptomatic and was able to engage in hard physical labor as a laundry worker. At last report 11 months after operation, she was still well.

Comment

The patient in this case had in pronounced degree vertebral artery insufficiency, headache and vestibular and visual disturbances, as well as numbness, paresthesias and claudication of the upper extremities. In addition, as a result of the syphoning of carotid flow through the vertebral system, the patient had slow mentation and difficulty in recall.

It was obvious that the posterior communicating system must be open, and, further, that both vertebral arteries communicated with the basilar system. The symptomatic state following operation on the left side and the relief of the symptoms by operation on the right side further illustrated that while unilateral vertebral artery occlusive disease is not ordinarily a symptomatic lesion, unilateral retrograde vertebral artery flow may well be.[2] The exceptions to this are cases of pronounced inequality in the size of vertebral arteries, and the unusual cases in which only one vertebral artery terminates in the basilar system. Internal mammary flow from one side to the other by way of collateral channel to the mediastinum has been previously described.[8] This pattern of flow was not possible in the present case because of bilateral subclavian occlusive disease. Thus, an additional route of collateral flow was demonstrated in this patient, namely, retrograde internal mammary artery to subclavian artery flow of aortic origin by way of mediastinal or pericardial branches.

The underlying cause of the symptoms in the

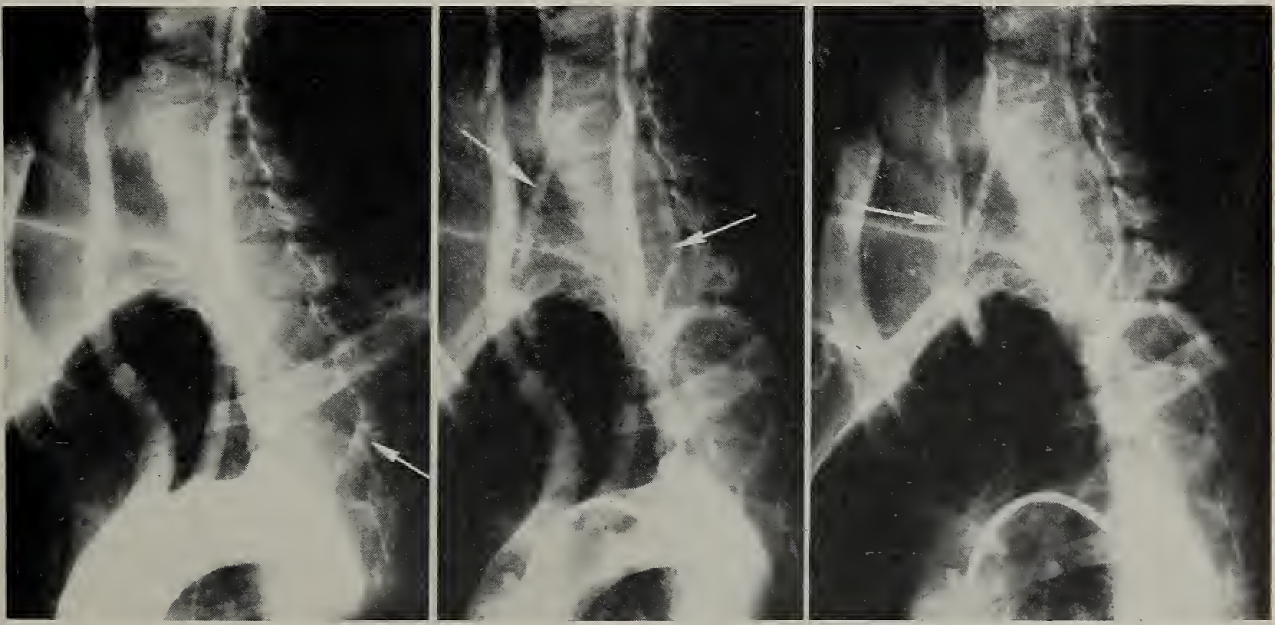

Figure 1.—*(Left)* a film taken early in the present case demonstrating carotid filling with occlusive disease at the bifurcations bilaterally. In addition, complete occlusion of the right subclavian artery and pronounced stenosis of the left subclavian artery is demonstrated. The arrow indicates early retrograde filling of the left internal mammary artery. *(Center)* in a later film, retrograde vertebral artery flow is indicated by the arrows with opacification of both subclavian arteries. *(Right)* in a still later x-ray film, persistent retrograde flow in the vertebral system was shown after carotid opacification had disappeared. The arrow indicates filling of the thyrocervical trunk.

present case was atherosclerosis. Occlusion of the first portion of the subclavian artery is almost exclusively due to this process. Other lesions, such as myofascial or osseous compression or arteritis more commonly involve the second or third portion of this vessel.[10] Subclavian steal has been reported as secondary to an embolus in this vessel.[5] In addition, congenital atresia of the subclavian artery or of the aortic arch distal to the left common carotid artery has been implicated.[7,3] No report could be found of a case in which the condition was secondary to arteritis.

The reason for electing to repair the left side first was that this would not involve any decrease in cerebral flow during operation. Staged repair seemed indicated to minimize the magnitude of the procedure. Clinical evaluation was, thus, also possible following repair of only one side. We chose an endarterectomy via the left transthoracic approach rather than a carotid to subclavian grafting procedure in the neck. One of several reasons for this was our reluctance to tap the common carotid artery proximal to an occlusive lesion at the carotid bifurcation. Further, we were impressed by data on the long-term patency of endarterectomized vessels and somewhat hesitant to use synthetic grafts in mobile areas. The right subclavian endarterectomy was approached through the neck. Very adequate innominate artery exposure may be obtained through this approach by subperiosteal resection of the clavicle. The patient in the present case had no impairment of shoulder girdle function following this procedure. After the vertebral artery flow was restored, carotid artery occlusive disease was an asymptomatic lesion.

Summary

A case of bilateral subclavian steal syndrome with symptoms of severe vertebral basilar insufficiency is presented. Occlusive lesions, involving the first portion of both subclavian arteries, were present. Successful staged endarterectomy was performed.

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Intrarenal Arteriovenous Fistula Following Needle Biopsy of the Kidney

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ARTERIOVENOUS FISTULA is a rarely reported complication of needle biopsy of the kidney but there is good reason to believe that it will be recognized more frequently in the future. Although this complication has been reported formally in the literature in only four cases[2,3] the authors know of five other recognized instances of arteriovenous fistula following needle biopsy.[5,7,10,12] The purpose of this paper is to present another case of intrarenal arteriovenous fistula following percutaneous needle biopsy. The lesion was suspected when an abdominal bruit was heard, was diagnosed by angiographic demonstration of the communication and was treated successfully by mid-segmental resection of the kidney.

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Report of a Case

A 35-year-old white man with diabetes was admitted to the UCLA Hospital 4 December 1963. Juvenile diabetes mellitus, discovered at age 17, had been controlled with 40 units of NPH insulin a day until two years before the present admittance, when an episode of coma occurred. The insulin dosage was increased and control was restored.

Four months before the patient was admitted he had had rapid onset of leg edema and swelling of the hands and face. At that time proteinuria was found and a percutaneous needle biopsy of the right kidney was performed through the back. The microscopic appearance was compatible with Kimmelstiel-Wilson's disease. The biopsy was not remarkable otherwise and no fragments of large vessels were seen in the specimen. Two months after the biopsy the patient began to experience easy fatigability and shortness of breath on exertion. On examination a continuous murmur was heard in the right upper quadrant and right flank.

At the time of admission to hospital the blood pressure was 150/78 mm of mercury and the pulse rate was 82. The eye grounds appeared normal. A continuous murmur with a strong systolic accentuation was heard in the abdomen. No masses or tenderness were detected in the abdomen or flank.

Laboratory data included fasting blood sugar of 279 mg and 350 mg per 100 ml on successive days. Blood creatinine was 1.4 mg per 100 ml and serum electrolytes were within normal range. Urinalysis showed 2 plus protein, no acetone and 12 leukocytes per high power field. Some hyaline casts were present. A culture of urine taken at midstream grew Klebsiella-aerobacter, over 20,000 per milliliter.

An electrocardiogram was within normal limits. A direct brachial artery pressure tracing was consistent with a hyperkinetic circulatory state. Cardiac output was 8.7 liters per minute on one determination and 9.1 liters on a second study. An intravenous urogram was normal with symmetrical appearance of the contrast medium in the rapid sequence films, equal concentration of the medium in the calyces and pelves and no evidence of segmental renal atrophy. Aortograms and selective renal arteriograms showed conditions diagnostic of an arteriovenous fistula. The fistula was in the anterior portion of the kidney in the lower middle segment and involved an interlobar artery and vein. An aortogram showed a double renal artery to the right kidney and a single artery on the left (Figure 1). The interlobar artery feeding the fistula was dilated and there was immediate filling of the veins draining this segment (Figure 2). Within one to two seconds of the selective injection of dye into the anterior renal artery (double renal arterial supply to the right kidney) there was filling of the main renal vein and vena cava (Figure 3 and 4). Selective injection of the renal artery supplying the posterior segment of the kidney did not disclose any abnormal arteriovenous communication (Figure 5).

Because it was felt that this arteriovenous fistula was responsible for high cardiac output and that it might have been responsible for the patient's symp-

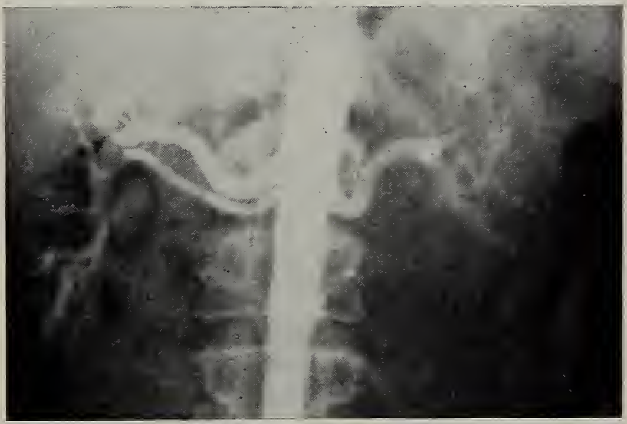

Figure 1.—Preoperative transfemoral catheter aortogram showing duplex renal arteries on right side and single left renal artery.

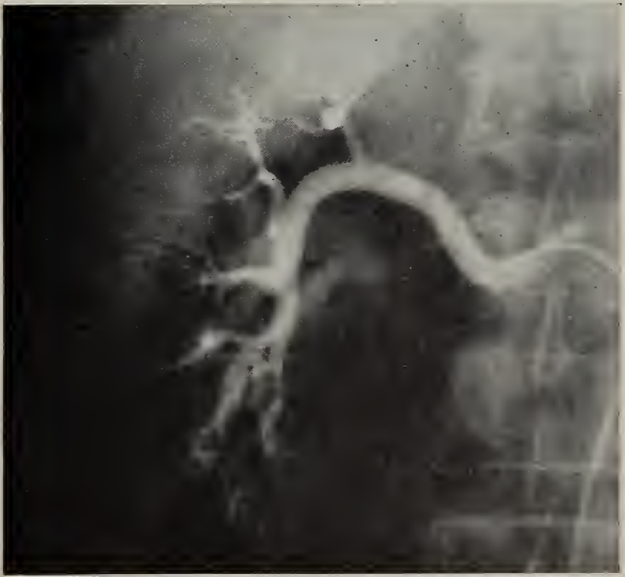

Figure 2.—Selective right renal arteriogram after placement of the catheter in the renal artery supplying the anterior surface of the kidney. Note the dilated interlobar branches in the lower segment.

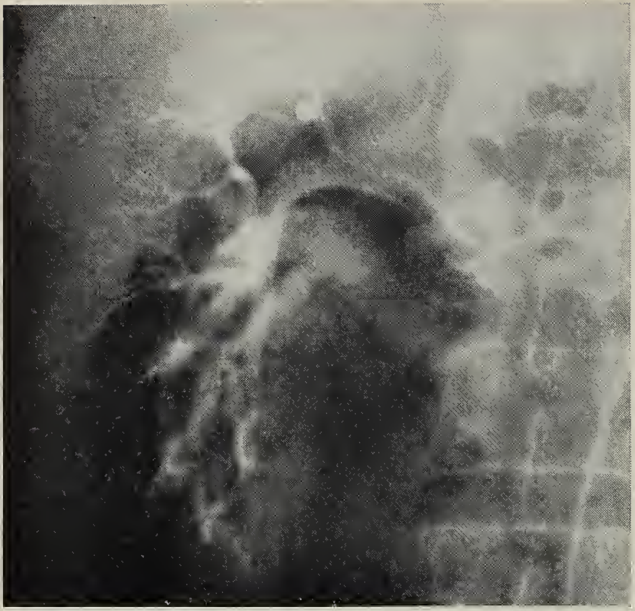

Figure 3.—Later phase of selective renal arteriogram showing filling of the renal veins after the injection of contrast medium in the renal artery.

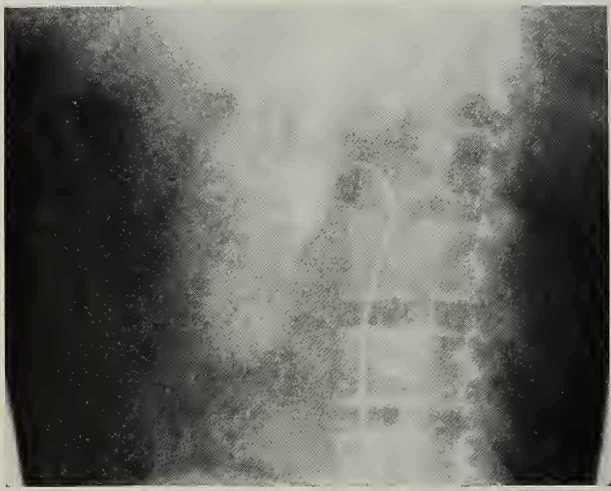

Figure 4.—Later phase of selective right renal arteriogram showing nephrogram and filling of the inferior vena cava.

toms of dyspnea and fatigability, surgical treatment was carried out. The kidney was approached through the right flank between the 11th and 12th rib. A stethoscope was used during the operation to determine the site of the murmur. The primary branches of the anterior right renal artery were dissected free in the region of the sinus renalis and individual branches were temporarily occluded in sequence while the kidney was monitored with the stethoscope in order to determine when the murmur was controlled by the individual arterial occlusion. When the arterial trunk supplying the anterior middle segment of the kidney was located

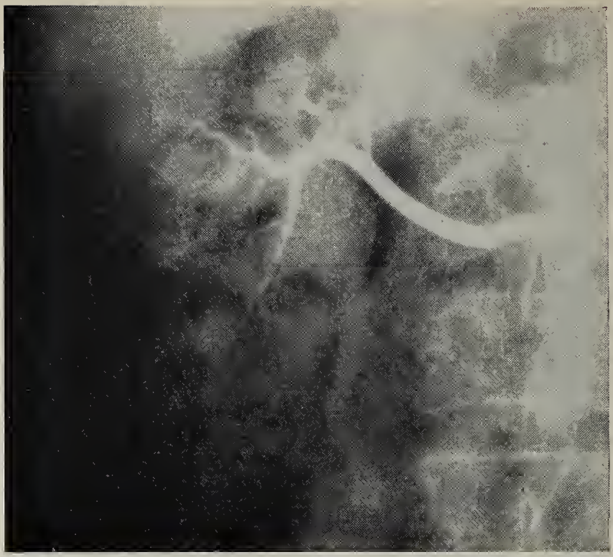

Figure 5.—Selective renal arteriogram (artery supplying posterior surface of the kidney). There is no venous filling after injection of this accessory renal artery.

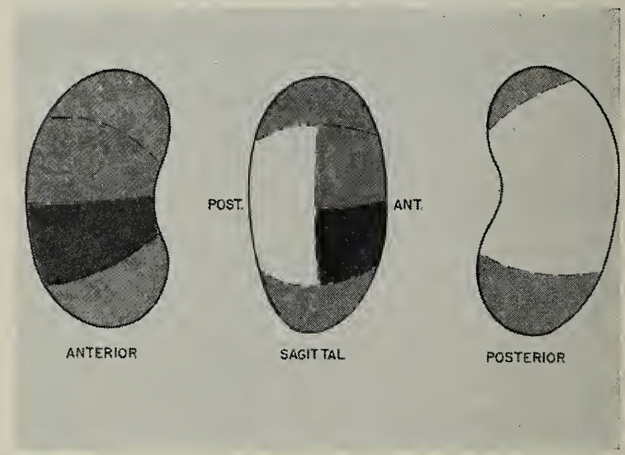

Figure 6.—Schema of renal segments according to common patterns of blood supply.

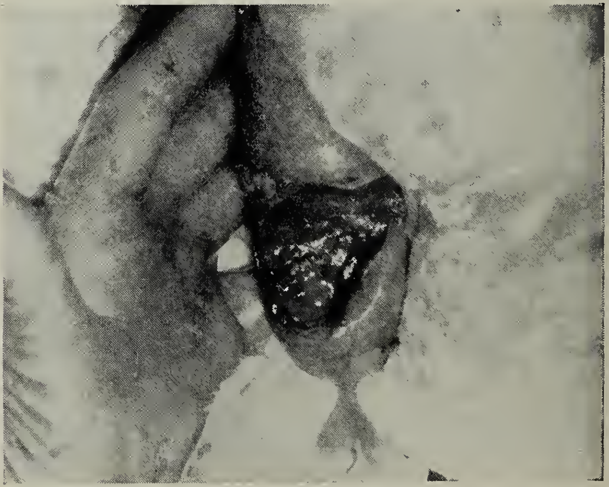

Figure 7.—Photograph of kidney at operation, showing resection of the anterior inferior middle segment of the kidney.

(Figure 6), the branch was ligated and two ml of indigo carmine was injected distal to the ligature, staining that segment a bluish hue. A segment of the kidney extending from the anterior surface down to and including the arteriovenous communication (Figure 7) was removed. The capsule was closed over the defect in the kidney and the patient made an uneventful postoperative recovery.

At last report, 17 months after operation he still had 2 plus proteinuria and the blood pressure was 150/80 mm of mercury but he had more energy and less fatigability. The abdominal bruit was no longer audible. Selective arteriograms that were made a year after operation showed an obliteration of the vessels supplying the anterior middle segment of the kidney and no evidence of arteriovenous fistula (Figure 8).

Discussion

Intrarenal arteriovenous fistula has been reported some 38 times in the literature. Gold and coworkers in 1965 collected 29 cases and reported one of their own. The following cases may be added to that series: two cases (reported by Blake[2]) following needle biopsy; one by Vest[14] after nephrolithotomy; one following partial nephrectomy, reported by Snodgrass and Robinson[13]; and four additional congenital cases.[1,4,9,16] Of these fistulas 21 were congenital, 12 occurred following trauma and five were secondary to renal carcinoma. Five additional cases of intrarenal arteriovenous fistula of the kidney have been alluded to in the literature.

Boijsen and Kohler[3] reported two cases of intrarenal arteriovenous fistula following needle biopsy. Diagnosis was made by selective renal angiography. Both patients had nephrosclerosis. One was treated by resection of the lower pole of the kidney, the other by ligation of two arteries leading into the fistula. Blake and coworkers[2] also reported two cases which were diagnosed by renal angiography, but neither of the patients was treated surgically. Another case in which lower pole resection was carried out was shown in a motion picture by MacKinnon.[10] The case herein reported had features similar in many respects to those of cases already reported. However, the method of treating the fistula was unique: Partial nephrectomy was performed after the vessel leading to the fistula was ligated, but the portion of kidney removed was the anterior inferior middle segment.

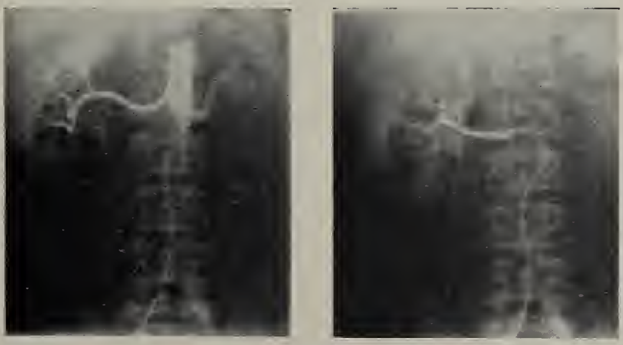

Figure 8.—Selective right renal arteriogram a year after operation, showing catheterization of the anterior major renal artery (in left frame) and posterior main renal artery (right frame). Note absence of interlobar branch supplying the inferior middle segment and absence of venous filling after arterial injection.

Undoubtedly arterial fistula of the kidney following needle biopsy has occurred more often than it has been recognized. Two means of diagnosing this condition are now being more widely used: auscultation of the abdomen for a bruit, and angiography. When one considers the nature of the problem, it is understandable that arteriovenous fistulas occur. The juxtaposition of the arcuate arteries and veins and the interlobar arteries and veins favors the development of arteriovenous communications following puncture. The extremely high blood flow through these renal vessels also favors the formation of arteriovenous fistulae. The diffuse arterial disease within the kidney (nephrosclerosis) may also render the vessels inelastic and predispose to fistula formation. These facts together with the increasing practice of needle biopsy will undoubtedly be responsible for an increasing number of cases.

Arteriovenous fistula of the kidney may or may not produce renal atrophy or physiological hemodynamic alterations. There may be an area of renal ischemia distal to the area of the fistula which, if large enough, can be responsible for hypertension. Theoretically several physiopathological conditions may exist depending upon the size of the fistula. Arteriovenous shunting may be responsible for a hyperkinetic circulatory state (as in the present case) and ultimately it may result in cardiac failure. Because of the generous flow of blood through the kidney, as much as one-fourth of the renal blood flow (one-sixteenth of the cardiac output) may be shunted through an intrarenal arteriovenous fistula. The fistula may produce no symptoms if there is only a small area of ischemia and if the volume of shunting is small.

The principal diagnostic aids are auscultation of the flank for a bruit, and angiography. Intravenous urography may show segmental areas of renal atrophy but this is unusual. On angiography there is usually a widening of the arterial branches leading to the arteriovenous fistula and evidence of venous filling in the early post-injection films. An area of segmental atrophy in the nephrogram may be seen.

The treatment of arteriovenous aneurysms may be ligation of the artery or segmental or total nephrectomy. In some cases non-intervention is the wisest choice. The size and location of the fistula should determine the need for a particular therapy. Wherever possible kidney parenchyma should be preserved. We believe that ligation of the vessel may be adequate but that it is preferable to resect the portion of the kidney supplied by the affected vessel.

Summary

Intrarenal arteriovenous fistula following needle biopsy of the kidney was diagnosed by selective angiography following the detection of an abdominal bruit. It was treated by ligation of the primary branch of the renal artery leading to the fistula and by resection of the anterior inferior middle segment of the kidney.

Several factors predisposing to the formation of intrarenal arteriovenous fistula of the kidney after needle biopsy have been discussed. The number of such fistulae will be found to increase with widespread use of needle biopsy and common practices of abdominal auscultation and renal angiography.

ADDENDUM: Since the preparation of this manuscript, Vertes and coworkers of Cleveland have diagnosed arteriovenous fistulae of the kidney following needle biopsy in 11 of 58 patients who had bilateral angiography after biopsy. In 8 of the 11 cases the fistula healed spontaneously and in three surgical treatment was necessary because of hemodynamic alterations that the condition caused.

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California Medicine

EDITORIAL

Medicare in 1966

Confronted last month with the fact of Public Law 89-97, the American Medical Association carefully examined its own great main purpose—to develop the best possible medical care and find ways of supplying it to all who need it—in the light of that new fact. From this examination came a statement of attitude that at once recognized the civic duty of respect for law and encouraged all physicians to keep constant vigil over bureaucratic rules and regulations that might diminish the quality of care or unduly encumber the processes by which it is rendered.

The statement, which was adopted at a special session of the AMA House of Delegates, pledged the AMA to advise with agencies of the Federal Government to the end that medicine's objectives on behalf of the public and the profession be preserved and where possible even advanced.

In view of the record of deterioration in the quality of medical practice in countries abroad where the state has come between physicians and their patients, it is quite understandable that physicians here are for the most part wary of anything that might lead down the same road in the United States.

This is not to say that we cannot hope to do better here than has been done in other lands. Indeed we begin under the new law with a note of hope in a statement made by John W. Gardner, the recently appointed Secretary of the Department of Health, Education, and Welfare. Dr. Gardner (Ph.D.), formerly president of the Carnegie Foundation for the Advancement of Teaching, said that implementation of Public Law 89-97 by his department will proceed "with due respect" for the integrity of the medical profession. Another reason for hope is that physicians with experience in practice and a thorough grounding in the ethics and the traditional aspirations of physicianship have been drawn into Federal Government positions in which they are certain to play a part in the shaping of Medicare. One of them is Philip R. Lee, of the Palo Alto Medical Clinic, who has become Assistant Secretary for Health in the Department of Health, Education, and Welfare. Another is Roberta F. Fenlon of San Francisco, a member of the Council of the California Medical Association, who has taken leave of her private practice to serve as Consultant to Arthur E. Hess, Director of the Bureau of Health Insurance of the Social Security Administration.

These auspices, however, cannot be expected to overcome the fundamental opposition of the great body of medicine to any system under which nonmedical third-party interference can fetter a physician's excercise of his best judgment in the treatment of his patients.

Whether or not to cooperate with the new Medicare program is for each physician to decide for himself, as the AMA statement of attitude makes plain. But whether a physician decides to take patients and payment under the Medicare law or declines to do so, from now on he ought to be alert for the good points and the bad in the system as it is set up, so that all the experience of individuals can be combined by the AMA as a force of intelligence for well directed negotiation.

As a medical organization we must at least annually review all our experience under Medicare to determine what effect the operation of the law is having on the quality of care, and thus be in position to recommend appropriate changes.

We anticipate that some physicians will readily take patients under Medicare, that some will take them with misgivings and that others will elect not to do so at all. We can hope that each of us will respect what each of the others decides and that schisms not develop along the lines of decision.

Need for Continuous Poliomyelitis Immunization

It can happen here! According to the morbidity and mortality report of the Department of Health, Education and Welfare, Public Health Service for the week ended 18 September 1965, an epidemic of poliomyelitis in Blackburn, Lancashire, England and in certain smaller contiguous communities has given rise to 50 cases. From these, Type I poliovirus was recovered and all of the patients were either unvaccinated or inadequately vaccinated. The first seven patients were under 20 years of age and they have persistent paralysis; of the remaining 43 patients, all adults, 17 were reported to have varying degrees of paralysis.

Mass immunization throughout the state of California has caused poliomyelitis practically to disappear. This will continue only if infants and children regularly receive poliomyelitis immunization, preferably by way of the oral vaccine. Children are the natural vectors of the disease; note that the first seven cases in Lancashire were all in patients under 20 years of age. There is far more importance in assuring the protection of young children than in attempting vaccination of adults, for thus the children are themselves protected and a considerable degree of protection from exposure is afforded to adults.

Precise necessities for "booster" administration of oral vaccine have never been completely worked out, but it is recommended that all children should have one dose of the trivalent oral vaccine at first school attendance in addition to primary immunization in infancy, as well as one dose of trivalent vaccine at the age of one year when immunization has been done in early infancy. It should be remembered that repeat doses of trivalent vaccine are quite without ill effect, because effective vaccination will permit infection of the gut only by one or another of the three strains against which immunity has not previously been established. Lifetime immunity is believed usually to follow immunization with Sabin vaccine but an occasional dose of the trivalent vaccine at wide intervals, especially throughout childhood and adolescence, would seem to be a safe and salutary method.

Edward B. Shaw, M.D.

Dr. Fenlon Goes to Washington

One of ours, near and dear to us, a member of the Council of the California Medical Association and a past president of the San Francisco Medical Society, has for the nonce relinquished the practice of medicine in San Francisco and gone to the nation's capital. We are speaking of Dr. Roberta F. Fenlon, who, upon the passage of Public Law 89-97 — "Medicare" — accepted appointment as Consultant to Arthur E. Hess, Director of the Bureau of Health Insurance of the Social Security Administration.

In her absence her practice will be attended to by an associate, but as all of us recognize who feel most comfortable when working as physicians, she is absenting herself at a considerable personal sacrifice.

We are pleased that she is willing to make that sacrifice, for Dr. Fenlon is well informed, realistic, logical and persuasive. Her work in Washington cannot but serve this nation and her profession well.

We are glad she went. We'll be gladder when she returns.

AMA Actions at Special Session

The following is the report of the Reference Committee on Legislation and Public Relations as amended and adopted by the AMA House of Delegates Special Convention, Chicago, 3 October 1965.

Mr. Speaker and Members of the House of Delegates:

Your Reference Committee recognizes the serious nature of the problems before this body and the decisions that must be made on this day—decisions which will affect the future of the practice of medicine for generations to come.

Your Committee heard 125 witnesses speak to 20 separate subjects during seven and one-half hours of testimony. Each witness spoke earnestly, forcefully, temperately, and with personal concern for the welfare of the patient in these United States.

Because of the the special nature of the subjects presented to this Special Convention and the interrelationship of the resolutions considered, your Reference Committee, in lieu of dealing with each resolution separately, has considered the intent and the language of all the resolutions. We believe it would be more expedient and practical to present for adoption by this House of Delegates a series of numbered comments, principles and policies which express the position of the American Medical Association on the issues under consideration.

Mr. Speaker, we have endeavored to evaluate, carefully and objectively, the matters before your Committee, and offer the following recommendations:

Physician-Patient Relationship

I. Physician-Patient Relationship. Public Law 89-97 affects the legal, traditional, and ethical concepts of the physician-patient relationship.

Legal counsel for the American Medical Association has stated that an individual physician acting independently and not in concert with others can lawfully refuse to accept any person as a patient who is a beneficiary under the program, or he may elect to treat such persons.

ACTION: Accepted for information.

In response to a request for an opinion by the Speaker, the Judicial Council, on 1 October 1965, rendered the following opinion:

The *Principles of Medical Ethics* are applicable to physicians when they engage in group action as well as when they act individually. Section 4 calls upon physicians to observe all laws. Accordingly, medical organizations must be mindful of the possible consequences of the actions they propose, engage in or encourage.

Under ordinary circumstances, the individual physician acting independently, is ethically free to select his patients. (See Section 5 of the Principles.) (a) He may decline to render medical services to persons covered by the "Health Insurance for the Aged Act." (b) He may choose to treat such persons without charge. (c) He may treat patients with the advance understanding that he will look to them exclusively for payment and that he will or will not in any way help them in obtaining reimbursement for the cost of his services or the cost of associated services.

However, under some circumstances, the physician's freedom to select his patients may be circumscribed by overriding ethical considerations. For example:

1. A physician should respond to any request for his assistance in an emergency.
2. Once having undertaken a case, the physician should not neglect the patient, nor should he withdraw from the case without giving notice sufficient to allow the patient to obtain another physician.
3. If a physician decides not to participate in the Medicare program or decides to limit his participation, he should so advise the patient in advance of treatment. This applies to services rendered by the physician as well as hospital services and other benefits provided under the program.
4. As provided in Section 1 of the *Principles of Medical Ethics,* a physician should not refuse to render medical services to any person if as a result such person will be unable to get necessary medical care.

It should be noted also that section 6 of the Principles provides that "A physician should not dispose of his services under terms or conditions which tend to interfere with or impair the free and complete exercise of his medical judgment and skill or tend to cause the deterioration of the quality of medical care." If after regulations are promulgated and the Medicare law becomes effective, the individual physician acting independently and not in concert with others, finds it does tend to impair the free and complete exercise of his medical judgment and skill or to cause a deterioration of the quality of medical care, the individual physician would be justified under this Principle in not participating under the law. The physician is ordinarily free to select his patients, subject to such ethical limitations as previously stated in Section 6 of the *Principles of Medical Ethics,* the Bauer Amendment, and in keeping with the nine principles for standards of health care programs adopted A-1965.

ACTION: Accepted for information.

In accepting the Judicial Council's opinion, as reported by the Reference Committee, the House called attention to the fact that this opinion should be read together with the Bauer Amendment (A-1961) and the nine principles for standards of health care programs adopted A-1965; and that these two items be distributed with the Judicial Council's opinion on the ethics involved in physician participation or non-participation in the Health Insurance for the Aged Act.

Mr. Speaker, your Reference Committee believes that it is desirable for this House to adopt a statement of policy regarding the traditional physician-patient relationship as it relates to Public Law 89-97. Mr. Speaker, we recommend that the following statement be adopted:

The American Medical Association opposes any program of dictation, interference, or coercion, whether direct or indirect, affecting the freedom of choice of the physician to determine for himself the extent and manner of participation or financial arrangement under which he shall provide medical care to patients under Public Law 89-97.

ACTION: Adopted as amended.

Regulations Under Public Law 89-97

II. Regulations Under Public Law 89-97. It was clear from the testimony received by your Reference Committee that the medical profession has a vital interest in the regulations which are to be promulgated under Public Law 89-97. Hastily drawn, unrealistic regulations could aggravate even further the undesirable effects of this law. Mr. Speaker, we recommend the adoption of the following statement as the present position and policy of the American Medical Association:

(a) The American Medical Association shall continue to meet with representatives of agencies and departments of the Federal Government, to participate in such advisory committees which are created, and to contribute whatever advice and suggestions are deemed advisable and necessary in the formulation and revision of regulations which will help it achieve Medicine's objectives on behalf of the public and the profession.

(b) The American Medical Association urges every physician, regardless of the extent of his involvement, to render whatever advice and assistance he can so that regulatory changes and/or legislative modifications may be suggested or sponsored by the American Medical Association in order that the best interests of the public and the profession may be protected in the provision of medical care.

(c) This House of Delegates expresses confidence in the Board of Trustees of the American Medical Association, its Advisory Committee, and the three-man Consultant Committee on Public Law 89-97 for their continuing efforts to secure regulations which are in the best interests of good patient care.

ACTION: Adopted as amended.

Related Items

Mr. Speaker, your Reference Committee next considered a number of items related to the primary subjects under consideration:

III. Certification by Physicians. Your Reference Committee recommends the adoption of the following statement of policy:

Current practices and customary procedures with respect to certification for hospital admission and care shall be continued under Public Law 89-97. The AMA Advisory Committee and the Association representatives to the technical advisory committees are advised to seek to accomplish this objective.

ACTION: Adopted.

IV. Blue Shield as Intermediary. Regulations yet to be promulgated will identify the nature of intermediaries under Public Law 89-97. Your Committee offers the following statement:

Blue Shield has, in many areas, demonstrated its ability to provide a competent insurance program. However, the AMA should leave to the state or appropriate local medical society, as the case may be, the expression of any preference for selection of a carrier.

ACTION: Adopted.

V. Reasonable Fees. Concern was expressed with respect to possible disputes between physicians and carriers relative to reasonable fees under the provisions of Public Law 89-97. We recommend the following statement of policy:

In the event of a dispute between physicians and carriers with respect to reasonable, customary, or usual fees, such disputes shall be resolved with the participation of the appropriate local medical society.

ACTION: Adopted.

VI. Utilization Review. Differences of opinion as to the purpose of utilization review committees were expressed. However, there was general agreement that with respect to the composition of such committees, the limitation of membership to include only physicians is preferred. Accordingly, we recommend the following statement to the House: Hospital utilization review committees shall be composed of practicing physicians.

Action: Adopted as amended.

Your Reference Committee understands that the Council on Medical Service will conduct a conference on the subject of utilization review committees on 27 November in Philadelphia. Recognizing the importance of this subject matter, your Reference Committee recommends that Resolutions No. 8, 18, and 35 be referred to the Council on Medical Service with instructions that the Association's Advisory Committee as well as the Board of Trustees and the House of Delegates be kept informed of developments in this area.

ACTION: Adopted.

VII. Compensation for Medical Services. Your Reference Committee believes that the physician should be informed fully as to the merits and limitations of billing patients directly for services, or accepting an assignment to enable payment by a federally designated fiscal intermediary, so that the physician can decide for himself in each instance the method of compensation which he prefers. We recommend that the Association take appropriate action to inform physicians regarding the options of payment for services available to them under the law and its regulations.

ACTION: Adopted as amended.

VIII. Shortage of Hospital Beds. The Oregon Delegation requested a survey of the probable shortage of hospital and related facility accommodations which may occur as a result of the implementation of Public Law 89-97. It also called for the development of a mechanism under which sufficient accommodations for the acutely ill, injured, or those in need of elective procedures will be reserved.

It is your Reference Committee's understanding that this subject is under active consideration by the Council on Medical Service. Your Committee accordingly recommends that this matter be referred to the Council for appropriate action.

ACTION: Adopted.

IX. Legal Opinion by AMA Counsel. Your Reference Committee was greatly impressed by the candid, forthright presentation by Mr. A. Leslie Hodson, legal counsel for the American Medical Association. We believe that his remarks should be made available to all constituent associations for their information and study. We believe that this will engender a better understanding of the legal limitations which face all medical organizations and the medical profession. Your Reference Committee recommends that the remarks of Mr. Hodson be distributed to the constituent associations.

ACTION: The House instructed the Board of Trustees to implement this action at the earliest possible date.

X. Non-Discrimination Under Federally Assisted Health Care Programs. Witnesses testified that a number of state agencies require pledges of non-discrimination for the ostensible purpose of meeting the requirements of title VI of the Civil Rights Act. Comments received were justifiably bitter in view of the profession's record of nondiscrimination in patient care.

Your Reference Committee has been informed that the Department of Health, Education, and Welfare has recognized the injustice of these state agency requirements and has recommended a substantial modification of this practice. Your Reference Committee believes that this matter should receive continuing surveillance.

ACTION: Although the Reference Committee recommended that this subject be referred to the Board of Trustees for continuing study by the Association's Law Department, the House did not concur and, in response to a motion from the floor, adopted Resolution No. 1. (See Page 361.)

XI. Separation of Professional Fees and Hospital Charges. Mr. Speaker, we offer the following statement of policy for consideration by the House:

Hospital-based medical specialists are engaged in the practice of medicine. The fees for the services of such specialists should not be merged with hospital charges. The charges for the services of such specialists should be established, billed and collected by the medical specialist in the same manner as are the fees of other physicians. The American Medical Association intends to continue vigorously its efforts to prevent inclusion in the future of the professional services of any practicing physician in the hospital service portion of any health care legislation.

ACTION: Adopted as amended.

Comments by Committee

Mr. Speaker, the policy statements herein presented to the House for its action are intended to respond to the specific problems placed before this Reference Committee. We are certain that more definitive statements on Public Law 89-97 will be adopted by this House as regulations are promulgated and as the program is implemented. But lest we be misunderstood, your Committee wishes to clearly emphasize that none of its recommendations should be construed as approval of Public Law 89-97, or in any way as acceptance of its philosophy.

Dr. James Z. Appel, in his remarks as President, told of his awareness of the problems before us. Dr. Appel spoke in his own behalf, but his comments reflect your Committee's feelings as well.

We congratulate him on his statesmanlike presentation, and we commend to each delegate the written transcript of his remarks.

Dr. Appel reminded us that, "Ours is a profession which must remain unified." "Ours is a profession which *must* remain unified," echoed many a speaker before your Reference Committee. These expressions of unity were voiced time and time again.

How shall we best maintain unity?

The Board of Trustees, in its report to this House, detailed in chronological order its efforts and experiences since the Annual Convention in June 1965. Your Committee heard many witnesses testify to the good work of the Board, to its devotion, and to its strength during these difficult times. To these unanimous expressions of confidence, your Committee adds its own. But we would not stop here. The leadership of the American Medical Association has been tested under fire. In difficult and crucial times, our officers and the Board have responded to legislative crises with courage and conviction. Years of withstanding the onslaught of the Medicare proponents did not weaken or lessen the determination of our officials.

The enactment of Public Law 89-97 would have come long before were it not for the leadership of our Board and Officers.

Nor should we fail to gratefully acknowledge the dedication, the inexhaustible effort, and the guidance provided by Dr. Blasingame and Dr. Howard, our Executive and Assistant Executive Vice Presidents.

We believe that the members of this House of Delegates would profit from a current report of the Association affairs, its programs, facilities, and personnel. Mr. Speaker, your Reference Committee recommends that Dr. Blasingame be invited to make such a presentation at the Clinical Meeting in Philadelphia.

ACTION: Adopted.

Mr. Speaker, before closing this report, your Committee would acknowledge some additional testimony received during the course of its hearing. Some speakers complained of inadequate knowledge of the activities of the Board, Councils and Committees of the Association. We believe that wherever the fault may be found, it must be shared by many. Undoubtedly, the Association should strive to continue to improve all means of communication available to it so that each physician member will be kept well informed on important matters. But each physician must be willing to receive the information beamed his way—through news releases, the weekly *AMA News,* and other AMA journals, publications, and communications. Finally, some of the fault must be shared by those state societies, or local medical societies, who at times receive the news from the AMA but fail to relay it to their members.

In Resolution No. 3 and in other remarks of witnesses, the Board and the House of Delegates were asked to consider the need for long-range planning. Your Committee believes that planning for the future should be an integral part of the activities of each AMA Council and Committee, as well as of the Board. While we realize that planning is a continuing and on-going program in the AMA, we would urge that the Board of Trustees take steps to assure that efforts in this regard be stressed even more by the Councils and Committees. Society is in constant flux and the American Medical Association must be prepared to meet the challenge of our times.

In still other remarks, the need for active physician participation in political activity remains clear. Your Reference Committee recommends that the House urge constituent medical societies and physicians to support and assist AMPAC and local medical political action committees in their efforts to elect candidates to office who will help preserve the physician's right to the free and independent practice of medicine.

In conclusion, Mr. Speaker, the members of your Reference Committee have been privileged to act in the capacity assigned to them. We know that in these trying times, the physicians of America will stand together and serve together in the best interests of their patients.

As a point of personal privilege, Mr. Speaker, I wish to express my gratitude to each member of the Committee for his patience, and for his diligent effort in discharging the monumental task assigned to him.

Submitted by:

George J. Lawrence, Jr., M.D., New York
George W. Petznick, M.D., Ohio
Harvey Renger, M.D., Texas
John M. Rumsey, M.D., California
B. E. Montgomery, M.D., Illinois, *Chairman*

Resolution No. 1
Introduced by: Ohio Delegation
Subject: Pledge of Non-Discrimination

Whereas, the Department of Health, Education, and Welfare has attempted to force physicians treating patients under federally-assisted programs to sign pledges of non-discrimination; and

Whereas, physicians, by subscribing to the Principles of Medical Ethics, willingly pledge to render service unconditionally to all patients with full respect for the dignity of man, providing for each a full measure of service and devotion, including in time of war the provision of medical care to the captured enemies of our country; and

Whereas, these conditions willingly self-imposed by the medical profession far exceed any pledge of this nature demanded by a Federal bureaucracy; therefore be it

Resolved, That all physicians are hereby informed that the refusal to sign such an oath does not flout the law; and be it further

Resolved, That the House of Delegates directs the Board of Trustees and the Officers of this Association to oppose actively and forcefully this and any future attempts by HEW or any other Federal agency to impose conditions and pledges upon the medical profession.

A Psychiatric Service for Adolescents

JOSEPH D. TEICHER, M.D.
Los Angeles

After many years of obvious need, an Adolescent Inpatient Service for emotionally disturbed young people was opened on July 15, 1964, in the Psychiatric Unit of the Los Angeles County General Hospital. Much planning and energy went into fulfilling this community need, particularly on the part of the hospital authorities, Dr. Edward Stainbrook,* and the Child Psychiatry Unit.

Physical Facilities

The eighth floor, on which the service is located, is a long straight corridor with rooms opening to the right and left. Formerly used for occupational therapy, meeting rooms and school, it was remod-

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The author is professor of psychiatry (Child), University of Southern California School of Medicine, and director of children's and adolescents' psychiatric services, Los Angeles County General Hospital.

*Professor and Chairman, Department of Psychiatry, University of Southern California School of Medicine; Chief Psychiatrist, Los Angeles County General Hospital.

eled into two wards, one for males, one for females, divided by a foyer and the nursing station. Each ward has beds for a maximum of eight adolescents and each is divided into two, three, or four bed occupancy with a maximum of privacy. There are attractive, individual bedstands, bureaus and bedside lights. Portable low dividers are to be installed between the beds. Chairs, draperies and painting are cheerful and the emphasis is on individuality. A recreation room is spacious and well furnished. The dining area, which has four tables seating four each, is used also for the high school and occupational therapy. It is a generally popular area for informal meetings of every variety near the coffee urn.

The wards are open. The one restraint is that the elevator floor signal buttons have been replaced by a switch requiring a key. Unless a youth is in a closed, locked ward, he can run away if he really wishes to do so. The open wards are indeed that, but, of course, limited to the eighth floor.

Types of Patients

Each patient proposed for admission is evaluated on the merits of the case and the composition of the ward at the time is an influencing factor. In most instances, patients with gross retardation, pronounced cerebral organic disease or a long standing history of destructive, acting out behavior are not acceptable. The stipulated age range is from 13 to 18; but as a practical matter persons beyond age 16 may not be admitted to the Adolescent Unit unless they are less mature than they might be expected to be and their problems are such that they can fit into the ward population. On the other hand, a mature 12-year-old girl was admitted.

Admission Procedures

There are no direct admissions to the Adolescent Ward. Processing of potential admissions, whether referred from a community agency or from the Psychiatric Unit Admitting Room, is done via the Child Psychiatry Outpatient Unit. We have devised a quick application, information-gathering and screening process. An admissions evaluation committee makes the decisions.

Where a young person is eligible and there is no bed space, every attempt is made to "carry" the patient in one of the outpatient clinics.

Ward Operation

The staff psychiatrists meet regularly with the nursing and ward attendants staff to exchange knowledge about adolescence and behavioral phenomena related to that period. The charge nurse meets daily with the young patients to discuss whatever they wish to talk about—recreation plans, complaints, suggestions and the like. The young people have their own group meetings and they help reenforce group standards on the ward. Collaborative work, shared information, informal meetings as well as weekly ward rounds—in which all members of the staff participate—and weekly treatment review conferences serve to keep all personnel informed and abreast of developments in each patient and the ward population as a whole. There is a regular school with two teachers from the Los Angeles City Schools System. Much emphasis is put on occupational and recreational activities, especially vigorous physical activities. A regular time is set for study, and ample time is provided for social activities. Questions as to whether patients may have visitors or passes are individually determined. A special on-call schedule of child psychiatry residents or staff is arranged, separate from the hospital on-call schedules.

Treatment

Duration of hospital stay is variable. There is no fixed termination date. The criterion is: "Has the patient (and his family) received maximum help from the inpatient experience?" Careful preparation for discharge and follow-up is as important as the hospital stay, whether discharge is to home or to a community facility. Incidentally, off-the-ward privileges are accorded to the young person as his capacity for autonomy and stress increase. Some youths may go to the neighborhood school or continue in their own school.

Close liaison with agencies is an absolute necessity for the success of the after-hospital care program. The role of the school and teacher is not only to teach and remedy educational deficits, but to coordinate the present curriculum with the home school's and facilitate reentry of the youth to his school society. A method of doing this has been worked out with the Los Angeles City Schools System.

Children's and Adolescents' Psychiatric Services, 1200 North State Street, Los Angeles, California 90033.

California Medical Association

NOTICES AND REPORTS

Council Meeting Minutes

Tentative Draft: Minutes of the 514th Meeting of the Council, San Francisco, Hyatt House, 18 September 1965.

The meeting was called to order by Chairman Anderson in the Hyatt House, San Francisco International Airport, on Saturday, 18 September 1965, at 9:30 a.m.

Roll Call

Present were President Teall, President-Elect MacLaggan, Editor D. L. Wilbur, Speaker Quinn, Vice-Speaker Telford and Councilors Isenhour, Wilson, Melone, Gooel, Bullock, O'Connor, Ham, Rogers, Maguire, Burnett, R. S. Wilbur, Miller, Watts, Fenlon, Anderson, Yant, Grunigen and Doyle. Absent for cause, Secretary Hosmer, Councilors Todd, Taw and Kaiser.

A quorum present and acting.

Present by invitation were Messrs. Hunton, Thomas, Clancy, Collins, Whelan, Miller, Clark, Klutch, Moreillon, Edwards, Bowman and Goldman, and Mmes. Griffith and Redfern of CMA staff; Messrs. Hassard and Huber of legal counsel; Messrs. Read, Salisbury, Putnam and Brown of the Public Health League; component society executives Rideout of Butte-Glenn, Baker of Los Angeles, Colvin of Monterey, Bannister of Orange, Walters of Riverside, Dochterman of Sacramento, Donmyer of San Bernardino, Neick of San Francisco, Marvin of Santa Barbara, Wood of San Mateo, Donovan and Pearce of Santa Clara, and York of Sonoma; Doctor Malcolm Merrill, state director of public health; Doctor Lester McDonald, medical director of the State Department of Social Welfare; Doctor William Thompson board chairman, and Messrs. Paolini, Babb, O'Dea, Nyron and Wahlberg of California Physicians' Service; Doctor Robert Radl of the State Department of Employment; Doctor Richard Young of the State Department of Rehabilitation; component society officers Edgar Wayburn of San Francisco, William Larsen and Howard Lindsey of San Mateo, Carl Goetsch of Alameda-Contra Costa and Ira Degenhart of Marin; Mr. Mark Berke of the California Hospital Association; Doctors Pierre Salmon, William O. Reinhardt and others.

1. *Minutes for Approval*

On motion duly made and seconded, minutes of the 513th Council meeting, held 7 August 1965, were approved.

2. *Membership*

(a) A report of membership as of 15 September 1965, was presented and ordered filed.

(b) On motion duly made and seconded, 32 delinquent members whose dues had been received were voted reinstatement.

(c) On motion duly made and seconded in each instance, five applicants were voted election to Associate Membership. These were: Rosemarie Lenel, Alameda-Contra Costa County; Luis Quan, Orange County; Savelly B. Chirman, Santa Barbara County; David N. Cook, Santa Clara County; Edward C. Halley, Santa Cruz County.

(d) On motion duly made and seconded in each instance, six applicants were elected to Retired Membership. These were: Edward Kupka, Alameda-Contra Costa County; G. Burch Mehlin, San Diego County; Fred S. Bruckman, Otto H. Pflueger, Harry A. Wycoff, San Francisco County; John F. Skelly, Santa Cruz County.

(e) On motion duly made and seconded, six members were voted a reduction of dues for reasons of illness or postgraduate study.

3. *American Medical Association*

Discussion was held on the special meeting of the House of Delegates of the American Medical Association to be held 2 and 3 October in Chicago. The need of a full representation of California delegates was agreed upon.

ACTION: Voted to assure a full representation of California Delegates but not to send Alternate Delegates unless their corresponding Delegates were unable to attend. All Delegates are to be polled to assure their presence for both days of the meeting.

4. *Adverse Drug Reactions*

Doctor Norman De Nosaquo, director of the Adverse Drug Reaction Registry of the American Medical Association, outlined the program of this department and urged the reporting of all reactions by practicing physicians.

5. *Report of the President*

President Teall reported on recent visits he had made to component societies and other gatherings.

Doctor Teall also discussed the implication of the Medicare legislation, Public Law 89-97 and reported on the activities of the Task Force established to review this legislation.

ACTION: Voted to approve in principle the outline of responsibilities of a Utilization Committee, as set forth by the Task Force. This statement reads:

A utilization committee should be organized and directed to consider the medical aspects of a case, not the economic aspects. It should ordinarily be a post-audit review patterned after existing tissue and record committees. Whenever feasible, it should be composed only of physician members of a hospital medical staff and responsible only to the medical staff and governing board of the hospital. County medical societies should be urged to coordinate the activities of utilization committees in their areas.

In regard to fees to be allowed under Public Law 89-97, the Task Force presented a statement which it urged be adopted as the policy of the Association. This statement reads:

The official position of the California Medical Association in discussions with the government and carriers will be to have them accept as the reasonable charge of a physician the usual and customary fee as that has been defined by the California Medical Association. Since the term "prevailing fee" may have a different meaning, CMA should urge the adoption of the concept of usual and customary fees as being the reasonable charge in California.

ACTION: Above statement adopted as the policy of the Association.

6. *Report of President-Elect*

President-Elect MacLaggan reported on county society and other visits he had made, including a Department of Public Health meeting on the "DeBakey Program" now before the Congress at presidential request. Changes in the legislation have made the program more palatable to physicians, he stated. Doctor MacLaggan also reported on the formation of the California Coordinating Committee for the implementation of the recommendations of the President's Commission on Heart Disease, Cancer and Stroke and stated that the Association would cooperate in the early planning stages through the use of funds from the Bureau of Research and Planning.

ACTION: Approved Doctors Teall, MacLaggan, Sherman and Mr. Klutch as CMA representatives on DeBakey Committee.

7. *Medical School Deans*

Doctor William O. Reinhardt, dean of the University of California medical school, reported that in 1966 the school year will be organized on a quarterly basis and that additional opportunities for students in the form of clinical clerkships and other training areas will be developed.

8. *State Department of Social Welfare*

Doctor Lester McDonald, medical director of the State Department of Social Welfare, reported that Mr. Jack Wedemyer, director of the department, and several associates had spent a week's time in Washington, learning details of the proposed operations of Public Law 89-97.

9. *State Department of Mental Hygiene*

Doctor James V. Lowry, director of the State Department of Mental Hygiene, reported that first admissions to state mental hospitals had decreased 10 per cent in number in the past five years, during which period the state's population had increased from 15½ to 18½ million. The daily census of state hospitals in this period has decreased 34 per cent.

Doctor Lowry also reported on two deaths in state hospitals from meningitis and a third case now under treatment. Cultures have been taken from other patients and staff members in the hospitals where these cases have appeared. Close cooperation with State Department of Public Health was noted.

10. *California Association of Nursing Homes, Sanitariums, etc.*

Doctor Pierre Salmon, chairman of the Committee on Health Care of the Aging, presented a report which had been reviewed by the Commission on Community Health Services and recommended by it for approval and publication. The report recommended that under county medical society sponsorship there be organized a medical staff equivalent organization to serve the nursing homes and other long-term care facilities in each community, that there be utilization and other committees to serve these institutions and that medical, nursing home and public interests be given representation on various committees.

ACTION: Report of Committee for Health Care of the Aging adopted as presented, including the guidelines in "The Physician and the Long-Term Care Facilities."

11. *California Hospital Association*

Mr. Mark Berke, president-elect of the California Hospital Association, reported that his organization has formed a committee on Medicare and hopes to have this committee meet with a counterpart committee of the CMA.

Mr. Berke was commended by the chairman on his recent election as a trustee of the American Hospital Association.

12. *California Physicians' Service*

Doctor William H. Thompson, board chairman of California Physicians' Service, reported that CPS has taken the initial steps to qualify as an administrator under Public Law 89-97. He also reported that the group of state employees which had been covered under the J schedule of fees had been denied a renewal of that contract and that the group is now covered under D and H fee schedules.

In regard to contract negotiations with the steelworkers, under a national Blue Shield coverage, CPS seeks policy determination by CMA on the concept of usual and customary fees as the prevailing fees for medical services.

ACTION: Voted to refer to the CPS Liaison Committee the question of evolvement of a prevailing fee concept and procedures to be followed under such.

13. *Department of Public Health*

Doctor Malcolm Merrill, director of the State Department of Public Health, gave a progress report on new responsibilities given the department under recent legislative acts. Fields to be covered will include alcoholism, PKU testing, mental retardation diagnosis and treatment centers, residential care for the mentally handicapped but physically able and the handling of draft rejectees.

Doctor Merrill also reported on an outbreak of typhoid fever in Madera County, which, coming on top of an epidemic of waterborne disease in Riverside county, has called for a statewide evaluation of drinking water supplies.

Chairman Anderson called the Council's attention to the fact that Doctor Merrill has resigned his state post in order to accept the post of coordinator of medical programs under the Department of State's AID programs. In recognition of Doctor Merrill's long tenure in state public health and his consistent cooperation with the Association, he was presented with a memorial plaque.

ACTION: Voted to adjourn today's meeting in honor of Doctor Malcolm Merrill and his long period of cooperation with the California Medical Association.

ACTION: Voted to recommend to House of Delegates the election of Doctor Malcolm Merrill as an Honorary member of the California Medical Association.

14. *Commission on Hospital Affairs*

Doctor Joseph Telford, in behalf of Doctor Bert Halter, chairman of the Commission on Hospital Affairs, reported on a meeting with a committee of the California Hospital Association, at which discussion was held on the advisability of entering into an agreement to participate in a pilot study, through data processing, on various facets of hospital planning. A federal grant of $10,000 would be available if matched by an equal amount contributed by the CHA and CMA. A motion to contribute $5,000 for this purpose was made and seconded but not acted upon.

ACTION: A substitute motion, to defer action on this proposal to the next meeting and to refer the matter to the Bureau of Research & Planning for study and report, was adopted.

15. *American Medical Association*

Doctor Dwight L. Wilbur, a Trustee of the AMA, outlined the program envisioned for the meeting called for 1 October 1965, on Public Law 89-97. He urged that the CMA adopt a positive program on this legislation, that it cooperate with the AMA in facing the new law and that cooperation also be given the AMA in regard to the proposed legislation on heart disease, cancer and stroke. Doctor Wilbur also urged that sound candidates for federal office be sought and supported in the 1966 elections.

16. *California Medicine*

Council acceptance of institutional advertising of the California Wine Advisory Board was requested. It was pointed out that CALIFORNIA MEDICINE now furnishes advertising representation to state medical journals in the other 11 western states and that this campaign was offered to the journals of these states.

***ACTION: Advertising of the California Wine Advisory Board voted approval for publication in* California Medicine.**

17. *Committee on Committees*

Chairman MacLaggan of the Committee on Committees presented a list of nominees to fill various committees. This list is attached and made a part of these minutes.

ACTION: Committee appointments as presented approved.

18. *Bureau of Research & Planning*

Reporting for Doctor Sherman, Mr. Klutch presented a bureau study on the Effect of Medical Discipline on Physicians' Practice.

ACTION: Study approved for distribution to component societies and to the State Board of Medical Examiners.

Mr. Klutch also listed several organizations which have requested copies of the second report of the Committee to Study the Role of Medicine in Society.

ACTION: Distribution of reports to above organizations approved.

19. *Committee on Legislation*

Mr. Ben Read of the Public Health League of California reported that the Committee on Legislation had requested staff members to meet with the legislative committees of the component societies and these meetings are under way. He also reported that the interim committees of the State Assembly had been named but no program of meetings yet announced; the interim committees of the State Senate have not yet been announced.

Mr. Read also reported that the special session of the Legislature, to discuss redistricting of the Legislature and the Casey Bill would convene on 20 September.

20. *Ad Hoc Committee on Workmen's Compensation*

Chairman Anderson, vice-chairman Miller assuming the chair, reported that the chairman of the Industrial Accident Commission had requested nominees in several fields of medical practice to serve as members of the Medical Advisory Committee of the commission. He listed the following names as nominations he had already proposed and stated that further nominations may be made if desired: Rutherford T. Johnstone, Occupational Medicine, General Preventive Medicine; Allen Jay Enelow, Psychiatry; Thomas Gucker, III, Orthopedic Surgery; Edgar Rosen, Internal Medicine; John C. Wilson, Jr., Orthopedic Surgery; Howard A. Brown, Neurological Surgery; Robert S. Hockwald, Internal Medicine; Clinton H. Thienes, Occupational Medicine; Knox H. Finley, Psychiatry; Vernon L. Nickel, Orthopedic Surgery; George C. Griffith, Cardiovascular Disease; Francis E. West, Orthopedic Surgery; William A. Newsom, Neurological Surgery; Gregory C. Murray, General Surgery, Plastic Surgery.

ACTION: Nominees as presented approved.

Doctor Anderson also outlined a proposed questionnaire to be sent out by the CMA to physicians as a means of determining their interest in treating workmen's compensation cases and their willingness to serve as independent medical examiners. These questionnaires would be returned to the component societies, which could then review the qualifications submitted by the respondents.

ACTION: Procedures as outlined by Doctor Anderson approved.

21. *Ad Hoc Committee on Medical Libraries*

Doctor Miller, chairman of the ad hoc Committee on Medical Libraries, reported that the committee has voted to reaffirm the medical library contribution in the current budget, had agreed to study two legislative bills now before the Congress to provide financial assistance to medical libraries and asked that the Council appoint a special committee to study the implications of these proposals and, if the measures are passed, to develop their implementation for medical libraries in California.

ACTION: Committee recommendation approved; Committee on Committees to name committee to study library support measures and propose implementation procedures.

22. *Commission on Community Health Services*

Doctor Kay, chairman of the Commission on Community Health Services, reported that the current "Health Tip" on babysitting, together with kits of forms to be used by parents, babysitters and babysitters' parents, had struck a responsive chord and that requests for the kit materials had been arriving at a rapid rate.

Doctor Kay also reported that the commission had voted to contribute, out of its budgeted funds, the amount of $700 to assist in the staging of a reception for guests attending a conference on air pollution sponsored by the AMA and the Los Angeles County Medical Association in March 1966.

23. *Legal Department*

Mr. Hassard reported that the state insurance commissioner had denied a permit to an out-of-state insurance carrier which had sought to issue policies in California to provide blood insurance. The proposed contract had been opposed by the blood banks on the state.

Mr. Hassard also reported on court decisions in Missouri and New York, in which widely varying opinions had been issued by trial courts concerning the rights of former osteopathic physicians and surgeons who have obtained Doctor of Medicine degrees in California in seeking hospital staff status.

24. *Medical Staff Surveys*

Mr. Goldman reported that 200 medical staffs of hospitals in 22 counties have been surveyed to date and that 103 of these have been granted full approval and 38 provisional approval. In the coming year it is hoped to complete an additional 130 surveys. About 90 per cent of the hospitals in areas where future surveys are scheduled have signified their wish to be surveyed.

Time and Place of Next Meeting

The chair announced that the next meeting would be held at the Airport Marina Hotel, Los Angeles on 30-31 October 1965.

Adjournment

There being no further business to come before it, the meeting was adjourned at 4:05 p.m.

CARL E. ANDERSON, M.D., *Chairman*
JOHN HUNTON, *Acting Secretary*

* * *

Committee on Committees—Report to the Council, 18 September 1965.

1. *Statewide Hospitals & Related Health Facilities and Services Planning Committee*—Six physicians were designated to be nominated for the two practicing physicians positions on this Committee. A vote seconding the nomination of Mr. Charles Abbott of Southern California Blue Cross to be representative of prepayment of health insurance programs on the Committee.

2. *Committee on Rural Health*—Doctor Franklin L. Murphy of Oroville was nominated.

3. *Veterans Board*—Doctor Robert S. Leake of Sacramento was recommended as a nomination for position of practicing physician on this Board.

4. *Committee on Disaster Medical Care*—Doctors Robert S. Johnson of Chico and Stephen Bruni of Fresno, both Regional Medical and Health Chiefs of the California Disaster Office were nominated as Consultants to this Committee.

5. *Liaison Committee to CMAA*—Doctors Richard H. Schug of Long Beach and Judith D. Smith of Vallejo were nominated to this Committee.

6. *Subcommittee on Venereal Disease*—Doctor Horrace F. Sharrocks was designated as Chairman to this Committee and Doctor Irwin Braff of San Francisco was designated as consultant.

7. *Ad Hoc Committee on Renal Dialysis Centers*—The following physicians were nominated to this Committee: Frank A. Gotch, San Francisco; Ralph Goldman, Morton H. Maxwell (chairman), Telfer B. Reynolds, Los Angeles; Allan M. Unger, San Francisco.

Continuing Medical Education

The Challenging Paradox of Rapid Medical Progress

GEORGE C. GRIFFITH, M.D.
Chairman of the Committee on Continuing Medical Education of the Scientific Board

BIOMEDICAL KNOWLEDGE is at present being generated at a rate which taxes the capacity of the physician to apply it to his daily practice. The physician finds himself in the paradoxial position of having increasing amounts of scientific information available to him and decreasing amounts of time in which to master it, sort it out, and make a judgment concerning its applicability to the problems he is called upon to deal with as a clinician.

To help the practicing physician meet this challenge, medical organizations at various levels are strengthening their resources for continuing medical education. California Medical Association is in the forefront of this movement.

To focus the attention of CMA members on this program, CALIFORNIA MEDICINE will devote a page bimonthly to new developments and new concepts in continuing medical education. This is the first of the series of pages. Others in the months to come will be contributed by spokesmen for medical schools throughout the state, by those responsible for educational programs in voluntary health agencies, and others who share with CMA the task of giving shape and order to continuing medical education.

CMA, through its Committee on Continuing Medical Education, contributes to both the shape and the order of the ongoing program. It believes that the primary responsibility for medical education, both undergraduate and postgraduate, rests with the medical schools, and it meticulously avoids usurping this role. All CMA programs of continuing medical education are developed in collaboration with the medical schools, and the content of these programs is determined by faculty members. CMA is, however, undertaking to act as catalyst in helping these schools augment their own postgraduate programs. The policy-making bodies of the various medical schools have been urged by the Committee to provide adequate operating budgets for the expansion of such programs.

A Clearing House for Program Information

To safeguard the orderly organization of medical education activities under all sponsorship throughout the state, the Committee this year has inaugurated a new service, its Office of Information, which serves as a clearing house for the scheduling of educational events. Since this is a new activity, CMA members may be interested in the mechanics through which it is carried out, and accordingly, we are reproducing the information form which we ask to have filled out by medical schools, voluntary health agencies, county medical societies, specialty societies, hospitals, and all organizations whose program of activities include education. This information is not only listed each month for six months in advance of the meeting in CALIFORNIA MEDICINE, but it is compiled into a new CMA publication, *Medical Dates Bulletin,* a master calendar which is being sent bi-monthly to all organizations participating in the clearing house.

The purpose of this coordinating service is to prevent conflicts in geography, time, and subject matter, and thus to conserve the time of the physicians who attend the meetings and the physicians who plan them.

REQUEST FOR SCHEDULE CLEARANCE OF CONTINUING MEDICAL EDUCATION
and listing in CALIFORNIA MEDICINE and *Medical Dates Bulletin*
(deadline: fifth of the preceding month)

FROM: ______________________________
(Organization) (Address)

My organization plans to offer a medical meeting or postgraduate course. Details are listed below. Please send me information on other meetings scheduled:

______________, ______________, ______________,
(week or month) (subject) (location)

so that we can avoid unnecessary conflict or duplication.

- -

Name of course or meeting ______________
Time and Date(s) ______________ Place ______________
Principal subject(s) ______________
(Please forward a copy of the program to CMA when it is ready)
Number of hours of instruction ______________ Fee, if any ______________
This course or meeting is scheduled annually: Yes ______ No ______.
If yes, please give specific dates and locations for: Next year ______________, ______________
Second year ______________, ______________ Third year ______________, ______________
Invitations to attend extended to: ______________
(Field or specialty) (Geographical area)
Contact for information: ______________
(Name and title) (Address)

In Memoriam

Allen, Martha Rinehart, Fairfax. Died 2 September 1965, in Reno, Nevada, aged 76. Graduate of the College of Physicians and Surgeons, Los Angeles, 1918. Licensed in California in 1918. Doctor Allen was a member of the Marin Medical Society.

◆

Austin, Ralph T., Van Nuys. Died 29 August 1965, in Encino, aged 41, of cancer. Graduate of the University of Utah College of Medicine, Salt Lake City, 1951. Licensed in California in 1951. Doctor Austin was a member of the Los Angeles County Medical Association.

◆

Campbell, Nell K., Montclair. Died 30 August 1965, in Montclair, aged 51. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1950. Licensed in California in 1950. M.D. degree from California College of Medicine, 1962. Doctor Campbell was a member of the San Bernardino County Medical Society.

◆

Clark, Elmer S., Long Beach. Died 6 September 1965, in Long Beach, aged 71, of lymphocytic leukemia. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1920. Licensed in California in 1921. M.D. degree from California College of Medicine, 1962. Doctor Clark was a member of the Los Angeles County Medical Association.

◆

Cole, George Carl, San Francisco. Died 17 September 1965, in Redwood City, aged 62, of heart disease. Graduate of New York University College of Medicine, New York, 1928. Licensed in California in 1950. Doctor Cole was a member of the San Francisco Medical Society.

◆

Cook, Alfred Lyman, South Gate. Died 6 September 1965, in an airplane crash near Ayumixtla, Mexico, aged 49. Graduate of the University of Nebraska College of Medicine, Omaha, 1940. Licensed in California in 1942. Doctor Cook was a member of the Los Angeles County Medical Association.

◆

Cowper, Herbert Hazlett, Los Angeles. Died 3 October 1965, in Pasadena, aged 53, of cerebral hemorrhage. Graduate of the University of Southern California School of Medicine, Los Angeles, 1939. Licensed in California in 1939. Doctor Cowper was a member of the Los Angeles County Medical Association.

◆

Crusan, Robert E., Monrovia. Died 29 August 1965, in Monrovia, aged 65. Graduate of the University of Pittsburgh School of Medicine, Pennsylvania, 1926. Licensed in California in 1928. Doctor Crusan was a member of the Los Angeles County Medical Association.

◆

Cummings, Roy Alfred, Santa Barbara. Died 22 September 1965, in Santa Barbara, aged 72. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1930. Licensed in California in 1930. Doctor Cummings was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Denenholz, Edward J., Modesto. Died 29 September 1965, in Modesto, aged 57. Graduate of the University of Illinois College of Medicine, Chicago, 1931. Licensed in California in 1945. Doctor Denenholz was a member of the Stanislaus County Medical Society.

◆

Edmeades, Willard Sefton, Martinez. Died 25 September 1965, in Martinez, aged 65, of coronary occlusion. Graduate of Washington University School of Medicine, St. Louis, Missouri, 1929. Licensed in California in 1929. Doctor Edmeades was a member of the Alameda-Contra Costa Medical Association.

◆

Glaser, Charles E., Auburn. Died 3 September 1965, in Auburn, aged 38. Graduate of Loyola University School of Medicine, Chicago, Illinois, 1949. Licensed in California in 1950. Doctor Glaser was a member of the Placer-Nevada County Medical Society.

◆

Gowern, Gerald Johnston, Arcadia. Died 17 August 1965, aged 48. Graduate of the University of Pittsburgh School of Medicine, Pennsylvania, 1940. Licensed in California in 1947. Doctor Gowern was a member of the Los Angeles County Medical Association.

◆

Haight, Warne L., Berkeley. Died 8 September 1965, in Berkeley, aged 60, of coronary occlusion. Graduate of Jefferson Medical College of Philadelphia, Pennsylvania, 1931. Licensed in California in 1944. Doctor Haight was a member of the Alameda-Contra Costa Medical Association.

◆

Heidenreich, Harry H., Arcadia. Died 22 September 1965, in Long Beach, aged 71. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1931. Licensed in California in 1931. Doctor Heidenreich was a member of the Los Angeles County Medical Association.

◆

Hendry, Edwin A., Sacramento. Died 22 September 1965, in Sacramento, aged 60, of heart disease. Graduate of the University of Oregon Medical School, Portland, 1932. Licensed in California in 1941. Doctor Hendry was a member of the Sacramento County Medical Society.

◆

Holmboe, Ruth Wade, Orinda. Died 26 April 1965, in Orinda, aged 50. Graduate of the University of Virginia School of Medicine, Charlottesville, 1946. Licensed in California in 1948. Doctor Holmboe was a member of the Alameda-Contra Costa Medical Association.

◆

Kawagoe, Haruko Harry, San Luis Obispo. Died 14 July 1965, in San Luis Obispo, aged 32. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1961. Licensed in California in 1962. Doctor Kawagoe was an associate member of the San Luis Obispo County Medical Society.

KEIPER, GEORGE FREDERICK JR., Visalia. Died 31 August 1965, aged 64, of subarachnoid edema. Graduate of the University of Michigan Medical School, Ann Arbor, 1925. Licensed in California in 1926. Doctor Keiper was a member of the Tulare County Medical Society.

✤

MORRIS, ROBERT GLYNN, Los Altos. Died 19 September 1965, in Los Altos, aged 45. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1948. Licensed in California in 1948. Doctor Morris was a member of the Santa Clara County Medical Society.

✤

PAULSEN, ERNST, San Francisco. Died 14 September 1965, in San Francisco, aged 70. Graduate of Medizinische Fakultät der Universität Wien, Wien, Austria, 1925. Dr. Paulsen was an associate member of the San Francisco Medical Society.

✤

PIERCE, GEORGE WARREN, San Francisco. Died 6 October 1965, in San Francisco, aged 76, of heart disease. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1914. Licensed in California in 1914. Doctor Pierce was a member of the San Francisco Medical Society.

✤

PRICE, HAROLD, Sherman Oaks. Died 29 September 1965, in Los Angeles, aged 59, of heart disease. Graduate of the University of Illinois College of Medicine, Chicago, 1935. Licensed in California in 1946. Doctor Price was a member of the Los Angeles County Medical Association.

✤

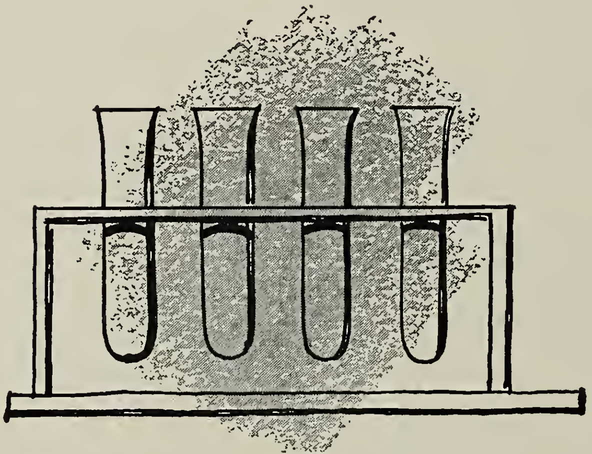
SAPPINGTON, EMMETT E., Sausalito. Died 10 September 1965, in San Francisco, aged 69, of heart disease. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1927. Licensed in California in 1927. Doctor Sappington was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✤

SHUTMAN, EDWARD E., Los Angeles. Died 26 September 1965, in Los Angeles, aged 41, of coronary artery disease. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1959. Licensed in California in 1959. M.D. degree from California College of Medicine, 1962. Doctor Shutman was a member of the Los Angeles County Medical Association.

✤

WALLERSTEIN, OTTO R., San Francisco. Died 4 October 1965, in San Francisco, aged 68. Graduate of Rheinische Friedrich-Wilhelms-Universität Medizinische Fakultät, Bonn, Prussia, Germany, 1921. Licensed in California in 1940. Doctor Wallerstein was a member of the San Francisco Medical Society.



PUBLIC HEALTH REPORT

MALCOLM H. MERRILL, M.D., M.P.H.
Director, State Department of Public Health

A simplified procedure for amending the medical and health data section on death, fetal death and live birth certificates has been established by recently enacted legislation.

It is now much less complicated for the certifying physician or coroner to make an amendment in the medical and health data originally reported on these certificates.

Whenever supplemental information becomes available making it necessary to modify information originally supplied, the certifying physician or coroner may now have the information amended by filing a simple statement to correct the record with the state or local registrar.

The record forms, with appropriate instructions, which are to be used in amending the health medical data sections of these certificates are available at the offices of the state and local registrars.

The Bureau of Occupational Health is conducting a comprehensive study of the effects of heat, noise and dust on the health of heavy equipment operators.

The study is the first of this type ever undertaken in the construction industry and is part of the Health Department's continuing program aimed at the prevention of work-induced disease and disability in California's labor force.

Cooperating in the study are the U.S. Public Health Service, the Operating Engineers Union and a number of private construction contractors.

The survey includes canal, freeway and other construction projects in the Sacramento and San Joaquin Valleys.

More than 60 legislative acts of public health interest were signed by Governor Edmund G. Brown and went into effect 17 September.

These included extension of the cancer quack law for two years; the establishment of a single statewide hospital and health facilities planning committee; the provision of toilet and handwashing facilities in food crop harvesting fields, and the testing of newborn children to detect as early as possible phenylketonuria and other preventable heritable disorders leading to mental retardation or physical defects.

The department is also charged with the establishment of regional centers for diagnosis counseling and arranging for the care of mentally retarded children. The initial appropriation is $1,500,000.

A medical care program developed since 1963 at Saugus Rehabilitation Center near Los Angeles shows that the chronic alcoholic from skid row is far from being a hopeless candidate for rehabilitation.

The program has had a 76 per cent success rate with the first group of chronic drunkness offenders who had voluntarily sought treatment before discharge.

Of 61 released alcoholics who originally agreed to report for treatment at the Los Angeles County Health Department's alcoholism clinic, 54 are still in treatment, are not drinking and have not been rearrested.

We attribute the success of the program to close cooperation of the Saugus Center, the clinic, the sheriff, the Bureau of Public Assistance, the Salvation Army and the department's Division of Alcoholism.

CMA

ANNUAL SCIENTIFIC ASSEMBLY

MARCH 20-23, 1966

LOS ANGELES

current concepts in therapy

POINT AND COUNTERPOINT

featuring—

RENAL FAILURE
CORONARY ARTERY DISEASE
GASTROINTESTINAL HEMORRHAGE

- ***among the distinguished speakers presenting their "current concepts in therapy":***
  - CHARLES K. FRIEDBERG, M.D., Columbia University
  - BERNARD LOWN, M.D., Harvard University
  - BELDING H. SCRIBNER, M.D., University of Washington
  - OWEN H. WANGENSTEEN, M.D., University of Minnesota

A VARIETY OF EVENTS in addition to those directly related to this year's theme WILL HIGHLIGHT YOUR 1966 ANNUAL SCIENTIFIC ASSEMBLY . . . eighteen medical specialty section meetings . . . seven special conferences . . . motion picture symposia . . . color TV programs . . . scientific and technical exhibits.

application for HOTEL ACCOMMODATIONS

NINETY-FIFTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • MARCH 20-23, 1966
BILTMORE HOTEL, LOS ANGELES

House of Delegates Opening Session Saturday evening, March 19: Scientific Programs begin Sunday morning, March 20.

1. Fill in the form below **completely** for room accommodations at the CMA's 1966 Annual Session. There is only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations must be made through the CMA Housing Bureau, 693 Sutter Street, San Francisco, California 94102.
4. **DEADLINE** for housing: March 4, 1966.

HOTEL ROOM RATES*

	Single	Double and Twins	Suites
BILTMORE HOTEL			
515 So. Olive Street	10.50-16.50	15.50-20.50	30.00-50.00
MAYFLOWER HOTEL			Triples
535 So. Grand Avenue	8.00-12.00	12.00-16.00	19.00
STATLER-HILTON			Suites
930 Wilshire Boulevard	10.00-17.50	16.00-22.50	30.00-65.00

*Rates subject to change

Send to: California Medical Association—*Housing Bureau*
693 Sutter Street, San Francisco, California 94102

Please reserve the following accommodations for the CMA's 1966 Annual Session in Los Angeles, March 20-23, 1966. The first meeting of the House of Delegates begins Saturday evening, March 19: Scientific Programs begin March 20.

Single Bedroom $.................... Twin-Bedded Room $.................... Double Bedroom $....................

Small Suite $.................... Large Suite $.................... Other $....................

First Choice Hotel.................... Second ....

Arrival (date) .... Hours .... a.m. p.m. Departure (date) .... Hour .... a.m. p.m.

THE NAME OF EACH HOTEL GUEST MUST BE LISTED. Include the names and addresses of both persons for each twin-bedded or double room, and names and addresses of all other persons for whom you are requesting reservations.

....

....

....

....

—PLEASE PRINT—

Your Name .... Officer? .... Delegate? .... Alternate? .... Speaker? ....

Address .... County ....

City and State .... Zip No. ....

WOMAN'S AUXILIARY

to the California Medical Association

It Can Happen Here

No one is immune to unexpected catastrophe. That is the reason for the existence of Physicians' Benevolence as an active committee in the Woman's Auxiliary to the California Medical Association complex. The Physicians' Benevolence Fund was established by the CMA in 1940 for the express purpose of "aiding needy members of the California Medical Association and their dependents."

For the fiscal year ended June 30, 1964, the fund received $27,680 income and made expenditures of $15,862. The excess of $11,968 went directly into reserves. Funds come from dues of each active physician in the CMA, from the Woman's Auxiliary and from interest from investments.

The fund is not set up as a retirement program or as an insurance plan. It is intended to serve as a temporary source of help. Application for such help is made through Mr. John Hunton, executive secretary of the CMA. This can be done by your own county's medical auxiliary Physicians' Benevolence chairman. An operating committee composed of Clyde L. Boice, chairman, and Drs. Elizabeth Mason-Hohl, Dudley Cobb, Alexander Fraser, Don C. Musser and George Wolf now administers the funds.

The Physicians' Benevolence Fund also contributes to the Los Angeles Physicians' Aid Association at the rate of $500 each month. This money is used to partially defray the costs of the Los Angeles Physicians' Aid Home and to help provide care for many needy eligibles outside the Home. The Home accommodates 36 persons. At present the majority are widows. Admission to the Home is made in the following order: (1) Members of the Los Angeles County Medical Society, (2) physicians who have practiced in Los Angeles County, (3) physicians who have practiced in California and have been members of their local medical society, and (4) physicians who have practiced in California. Widows and dependents fit under the husband's classification. Those who can afford to pay are charged for their board and room.

The goal of the Physicians' Benevolence Fund is to become self supporting. This is not possible unless much more money is given. It would take $500,000 at 4 per cent interest to provide the fund with $20,000 it needs in today's conditions. At present the fund is $73,320.

We are blessed in so many ways, let us each go the extra mile to help those less fortunate in our medical family. Let's make this year a 100 per cent year—$1 from every Auxiliary member. Really a small way to help our own.

Mrs. Joseph L. Pace
State Chairman
Physicians' Benevolence

NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

Merger of the California College of Medicine with the University of California was completed 1 October. The announcement was made by President Clark Kerr of the University and W. Ballentine Henley, Sc.D., who was President of the College and becomes Provost of the new campus. With the signing of the merger document, University Regents and College Trustees joined the two institutions.

In the same action, Warren L. Bostick, M.D., became Dean of the College, which is designated University of California, California College of Medicine.

Terms of the merger agreement between the Regents of the University and Trustees of the College, initiated last March, carry out the spirit of the California Legislature's intent, which provided for state support of the medical college as a regular part of the university.

The college is the university's second medical campus in the Los Angeles area. It has 352 undergraduate medical students taking the four-year training program leading to the M.D. degree.

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Southern California's new **Medical Television Network** linking over 50 hospitals via KCET, Channel 28, began 26 October with a program on rheumatoid arthritis. Weekly programs, coded ("scrambled") so that they can be viewed by medical personnel only, are planned.

This video education feature, presented by University of California Extension, will be co-produced by schools of medicine at UCLA, USC, California College of Medicine and Loma Linda University, KCET, the American Cancer Society, the Academy of General Practice and the City of Hope Medical Center.

The American Medical Association Committee on Motion Pictures, Radio and Television has endorsed the project.

UC Extension will install and maintain the special receiving sets in cooperating hospitals.

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Dr. Clayton G. Loosli, Hastings Professor of Medicine and Medical Director of The Hastings Foundation at the University of Southern California School of Medicine, has been elected chairman of **Los Angeles County Air Pollution Control District's** Scientific Advisory Committee. Dr. Loosli succeeds Dr. Reginald Smart, USC clinical professor of medicine. Dr. Hurley R. Motley, USC professor of medicine was elected committee vice-chairman.

The Scientific Advisory Committee meets bi-monthly for review and committee recommendations on problems brought to it by the staff of the Air Pollution Control District.

In addition to Drs. Loosli, Motley and Smart, committee members include Drs. Gordon R. Barclay, Francis E. Blacet, Ulric B. Bray, L. S. Goerke, A. J. Hagen-Smit, Thomas J. Haley, Morris Hein, Paul Highby, Walter E. Macpherson, Francis M. Pottenger, Jr., and George S. Sharp, and Mr. James W. Daily.

* * *

Dr. George J. Hummer of Santa Monica was elected president-elect of the **American Association of Blood Banks** and Dr. E. Arthur Dreskin of Greenville, South Carolina, was installed as president at the annual meeting held at Bal Harbour, Florida in September. The next meeting of this organization of community and hospital blood banks will be held 25 to 28 October 1966, in Los Angeles.

SAN FRANCISCO

Dr. Roberta F. Fenlon, San Francisco, a member of the Council of the California Medical Association and a past president of the San Francisco Medical Society, has been appointed Medical Consultant to Mr. Arthur E. Hess, Director of the Bureau of Disability and Health Insurance of the Social Security Administration, in Washington, D.C. Her work, which she has already begun, is concerned with benefits under the new medicare program of the Federal Government.

Dr. Fenlon expects to be continuously occupied, with her new duties for several months, then to return to her practice in San Francisco, which meanwhile is in the hands of an associate.

SANTA CLARA

Dr. LeRoy Allen Pesch, 34, professor and chairman of the department of medicine at Rutgers Medical School, has been appointed associate dean and professor of medicine at the **Stanford University School of Medicine.** The appointment was announced late last month by Stanford University President J. E. Wallace Sterling.

Dr. Robert J. Glaser, vice president for medical affairs and dean of the medical school, said "Dr. Pesch's experience in the problems of modern medical education will represent an invaluable asset to Stanford Medical School. As associate dean, Dr. Pesch will have major responsibility for all aspects of student affairs and will occupy an important liaison position between students and faculty."

GENERAL

A four-day **American College of Cardiology postgraduate course** will be presented 7 to 10 December 1965, at the Scripps Clinic and Research Foundation, La Jolla. The course is open to all physicians. Described as "an intensive postgraduate program in clinical cardiology offering a view of the field in 1965," the course has a guest faculty numbering nineteen.

Brochures listing faculty and subjects to be discussed may be obtained by writing to the Executive Director, American College of Cardiology, 9650 Rockville Pike, Washington, D.C., 20014.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Postgraduate Course Information

CMA:	**California Medical Association** For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. PRospect 6-9400, Ext. 68.
LLU:	**Loma Linda University** For information contact: W. F. Norwood, Ph.D., Assistant Dean and Chairman, Division of Continuing Education, Loma Linda University School of Medicine, 1720 Brooklyn Ave., Los Angeles 90033, ANgeles 9-7241, Ext. 214.
PRES. MED. CTR.	**Presbyterian Medical Center** For information contact: Arthur Selzer, M.D., chairman, Education Committee, Presbyterian Medical Center, Clay and Webster Streets, San Francisco 94115. WEst 1-8000.
UCLA:	**University of California at Los Angeles** For information contact: Charles R. Smart, M.D., Assistant Director, Continuing Education in Medicine and Health Sciences, UCLA Medical Center, Los Angeles, 90024, 478-9711, Ext. 2114.
UCSF:	**University of California, San Francisco** For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, University of California Medical Center, Room 565-U, San Francisco 94122, 666-1692.
USC:	**University of Southern California** For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, USC School of Medicine, 2025 Zonal Ave., Los Angeles 90033, 90033, CApital 5-1511, Ext. 300.
STAN:	**Stanford University** For information contact: Roy Cohn, M.D., Associate Dean for Graduate Affairs, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto, DAvenport 1-1200.

NOVEMBER

November 16-17—**Albert M. Snell Memorial Lectures.** Presented by the Palo Alto Medical Research Foundation. Palo Alto Medical Clinic Auditorium. Tuesday and Wednesday evenings at 8:00 p.m. Contact: Edward E. Daleske, assistant director, Palo Alto Medical Research Foundation, 860 Bryant St., Palo Alto.

November 17—**Santa Barbara Cottage and General Hospitals Program on Advances in Medical Practice.** Santa Barbara Cottage Hospital. Wednesday. 3 hours. Contact: C. A. Domz, M.D., 317 West Pueblo, Santa Barbara.

November 17-February 9—**Psychiatric Case Conferences-Section 2.** USC at Memorial Hospital of Long Beach. Wednesday evenings. 24 hours. $35.

November 19-20—**Fear and Pain Control: A Practical Approach.** UCSF. Friday-Saturday. $40.

November 21-24—**International College of Surgeons Southern California Division Western Regional Meeting.** Riviera Hotel, Las Vegas, Nevada. Sunday-Wednesday. Contact: F. M. Turnbull, Jr., M.D., secretary, 1127 Wilshire Blvd., Los Angeles 90017.

November 23-February 15—**Psychiatric Case Conferences-Section 4.** USC at Valley Presbyterian Hospital, Van Nuys. Tuesday evenings. 24 hours. $35.

November 28-30—**West Coast Allergy Society Annual Meeting.** Sheraton Palace Hotel, San Francisco. Sunday-Tuesday. Members: $15., Non-Members: $25. Contact: Executive Secretary, West Coast Allergy Society, P.O. Box 42067, Portland, Oregon 97242.

November 30-February 22—**Psychiatric Case Conferences-Section 5.** USC at Hawthorne Community Hospital. Tuesday evenings. 24 hours. $35.

DECEMBER

December 1—**St. Luke Hospital Annual Postgraduate Assembly.** St. Luke Hospital Staff Room, Pasadena. Wednesday. 8 hours. Contact: R. D. Miller, M.D., chairman, Annual Postgraduate Assembly, 615 East Union Street, Pasadena 91101.

December 1-March 2—**Psychiatric Case Conferences-Section 1.** USC. Wednesday evenings. 24 hours. $35.

December 1-March 2—**Psychiatric Case Conferences-Section 3.** USC at Santa Monica Hospital. Wednesday evenings. 24 hours. $35.

December 2-3—**Medicine Megalopolis.** USC at Ambassador Hotel, 3400 Wilshire Blvd., Los Angeles. Thursday-Friday. 16 hours. $25.

December 2-4—**California Society of Pathologists—Data Processing in Laboratory Medicine.** Disneyland Hotel, Anaheim. Thursday-Saturday. Contact: Weldon K. Bullock, M.D., 1200 N. State Street, Los Angeles.

December 2-4—**Microangiopathy of the Eye in Diabetes.** UCSF. Thursday-Saturday. 16½ hours. $75.

December 3-4—**Vectorcardiography.** UCSF. Friday-Saturday. 11½ hours. $40.

December 3-5—**Fluid and Electrolyte Balance.** USC at the Riviera Hotel, Palm Springs. Friday-Sunday. 15 hours. $60.

December 7-10—**American College of Cardiology Postgraduate Course.** Scripps Clinic and Research Foundation, La Jolla. Tuesday-Friday. Contact: Executive Director, American College of Cardiology, 9650 Rockville Pike, Washington, D.C., 20014.

December 7-March 1—**Psychiatric Interviewing in Medical Practice.** USC. Tuesday evenings. 24 hours. $35.

December 8—**Tuberculosis and Health Association of Alameda County Annual Symposium-Seminars on Respiratory Diseases.** Co-sponsored by the Alameda-Contra Costa Academy of General Practice. Berkeley House Hotel/Motel, Berkeley. Wednesday. 6 hours. Contact: E. Ronald Riggall, M.D., chairman, 121 E. 11th Street, Oakland.

December 11—**Medical Emergencies.** Pres. Med. Ctr. Saturday. 8 hours. $30.

December 11-12—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton, Saturday-Sunday. 12 hours. $10.

JANUARY

January 8—**Human Development and Birth Defects.** UCSF at Childrens Hospital, San Francisco. Saturday. 5½ hours. $15.

January 14-16—**A Time for Decision: The Biologic Crossroad.** UCSF. Friday-Sunday.

January 15—**Conference on Neurologic Evaluation.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 17-21—**Annual Mid-Winter Convention in Ophthalmology and Otolaryngology.** Statler Hilton Hotel, Los Angeles. Monday-Friday. Contact: Norman Jesbere, M.D., secretary treasurer, Research Study Club of Los Angeles, 1136 West Sixth Street, Los Angeles 90017.

January 18-April 12—**Medical Radio Conferences.** UCSF. Tuesdays, 12:30-1:30 p.m.

January 19—**Los Angeles County Heart Association Annual Midwinter Symposium.** Statler Hilton Hotel, Los Angeles. Wednesday. 6 hours. Contact: Harold Miller, M.D., chairman, Professional Education Committee, 2405 W. Eighth Street, Los Angeles 90057.

January 19—**Riverside County General Hospital Postgraduate Assembly.** Riverside County General Hospital. Wednesday. 12 hours. Contact: Harold A. Roth, M.D., Riverside County General Hospital, 9851 Magnolia Avenue, Riverside 92503.

January 19-April 20—**Psychotherapeutic Principles and Practice for Non-Psychiatrists.** UCSF. Wednesdays. 70 hours. $25.

January 19-May 18—**Teaching Clinics in Psychiatry.** UCLA. Wednesdays.

January 20-21—**New and Old Antibiotics.** USC. Thursday-Friday.

January 20-April 7—**Medical Radio Conferences.** UCSF. Thursdays, 12:30-1:30 p.m.

January 22—**Pediatric Cardiology Symposium.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 28—**Nuclear Medicine.** USC. Friday.

January 28-30—**Clinical Conference in Pediatric Anesthesiology.** Friday-Sunday. Contact: M. Digby Leigh, M.D., Childrens Hospital of Los Angeles, 4614 Sunset Blvd., Los Angeles 90027.

January 29—**Practical Proctology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 31-February 1—**Uroradiology.** UCLA. Monday-Tuesday.

FEBRUARY

Februrary 1-March 22—**Isotope Techniques in the Health Sciences.** UCSF. Tuesdays.

February 1-April 19—**Bedside Cardiology.** USC at Los Angeles County Hospital. Tuesdays.

February 2-4—**Aviation Medicine Seminars.** UCSF at Del Webb's Townehouse, San Francisco. Wednesday-Friday.

February 3-4—**SOUTHERN COUNTIES—Regional Postgraduate Institute presented by California Medical Association** in cooperation with USC School of Medicine. El Mirador Hotel, Palm Springs. Thursday-Friday "Hematology and Infectious Diseases and Antibiotics." Chairman: Robert M. Zweig, M.D., 3875 Jackson, Arlington.

February 4-5—**New Potentials in Diagnosis and Treatment.** UCSF. Friday-Saturday. 12½ hours. $40.

February 4-March 11—**Psychiatry in Daily Practice.** UCSF at Mercy Hospital, Redding. Fridays.

February 7—**Medical Aspects of Well Being: Emotional Aspects of Rehabilitation.** UCSF. Monday.

February 7-March 14—**Contra Costa County Heart Association Postgraduate Course for Physicians.** John Muir Hospital, Walnut Creek. Mondays. 12 hours. $15. Contact: Loyse C. Casebolt, executive director, 1541 East St., Walnut Creek.

February 9—**Symposium on Shock.** USC. Wednesday.

February 10-11—**Symposium on Endocrinology.** USC. Thursday-Friday.

February 10-12—**The Specialties in Pediatric Office Practice.** UCSF. Thursday-Saturday.

February 11-13—**American College of Physicians, Northern California and Nevada Regional Meeting.** Mark Thomas Inn, Monterey. Friday-Sunday. 10 hours. Contact: Roberto F. Escamilla, M.D., Governor, Northern California and Nevada Region, American College of Physicians, 897 Hyde Street, San Francisco.

February 12—**Surgical Emergencies.** Pres. Med. Ctr. Saturday. 8 hours. $30.

February 12-13—**Cystic Fibrosis.** UCLA. Saturday-Sunday.

February 12-13—**A Symposium on Hypnosis.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

February 12-13—**Law-Science-Medicine.** UCSF. Saturday-Sunday.

February 14-16—**Institute for Metabolic Research Dynamics of Endocrine and Metabolic Disease Annual Symposium.** Highland Hospital. Monday-Wednesday $30. Contact: L. W. Kinsell, M.D., director, Institute of Metabolic Research, 2701 14th Ave., Oakland.

February 14-18—**American College of Chest Physicians—Clinical Application of Cardio-Pulmonary Physiology.** Ambassador Hotel, Los Angeles. Monday-Friday. Contact: Alfred Goldman, M.D., program chairman, Suite 906, 9201 Sunset Blvd., Los Angeles 90069.

February 14-18—**Course for Physicians in General Practice.** UCSF at Mt. Zion Hospital, San Francisco. Monday-Friday.

February 16-20—**Controversial Areas in Surgery.** UCLA at Palm Springs. Wednesday-Sunday.

February 18-19—**Pediatric Dermatology.** UCSF. Friday-Saturday.

February 18-20—**American College of Physicians Southern California Regional Meeting.** Biltmore Hotel, Santa Barbara. Friday-Sunday. Contact: W. Philip Corr, M.D., governor, 3660 Arlington Ave., Riverside 92506.

February 19-20—**Neuropsychiatry in Daily Practice.** UCSF in Salinas. Saturday-Sunday.

February 20-23—**Current Concepts in Chemotherapy.** UCLA at Palm Springs. Sunday-Wednesday.

February 24-25—**Medical-Surgical Gastroenterology Conference.** USC. Thursday-Friday.

February 25-26—**Workshop on Hand Injuries.** Pres. Med. Ctr. Friday-Saturday. 12 hours. $75.

February 25-27—**Conference on Mental Retardation for Physicians.** UCSF. Friday-Sunday.

February 27-March 2—**Surgical Applied Anatomy.** LLU. Sunday-Wednesday. 29½ hours.

MARCH

March 2-3—**Los Angeles County Heart Association Annual Spring Symposium.** Statler Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hours. Contact: Harold Miller, M.D., chairman, Professional Education Committee, 2405 W. Eighth Street, Los Angeles 90057.

March 2-3—**Western Electroencephalography Society Annual Meeting.** Hilton Hotel, San Francisco. Wednesday-Thursday. Contact: Edward E. Shev, M.D., secretary treasurer, 516 Sutter St., San Francisco.

March 2-4—**American Medical Association Air Pollution Medical Research Conference.** Ambassador Hotel, Los Angeles. Wednesday-Friday. Contact: Air Pollution Medical Research Conference, Department of Environmental Health, AMA, 535 N. Dearborn St., Chicago, Illinois 60610.

March 3-4—**Symposium on Diabetes.** USC. Thursday-Friday.

March 4-5—**Gynecological Problems for the Non-Gynecologist.** UCSF. Friday-Saturday.

March 4-5—**Operable Heart Disease.** Pres. Med. Ctr. Friday-Saturday. 16 hours. $35.

March 5-6—**The Knee.** UCLA. Saturday-Sunday.

March 5-6—**Sexual Conflicts and Adjustments.** UCSF at Herrick Hospital, Berkeley. Saturday-Sunday.

March 9-11—**Conference on Keratoplasty.** Pres. Med. Ctr. Wednesday-Friday. 21 hours. $125. Contact: Lions Eye Foundation, Pres. Med. Ctr., 2018 Webster St., San Francisco 94115.

March 9-13—**Diagnostic Radiology.** UCSF. Wednesday-Sunday.

March 10-14—**Pulmonary Problems.** UCLA. Thursday-Sunday.

March 11-12—**Childrens Hospital Medical Center Annual Postgraduate Seminar and Clifford D. Sweet Lecture.** Childrens Hospital, 51st and Grove Streets, Oakland. Friday-Saturday. 8 hours. $30 for 4 sessions or $10 per session. Contact: Childrens Hospital Medical Center, Oakland.

March 11-12—**WEST COAST COUNTIES—Regional Postgraduate Institute presented by California Medical Association** in cooperation with UCSF. Ojai Valley Inn, Ojai. Friday-Saturday. "Indications for Surgical Intervention—The Difficult Decision." Chairman: George J. Wittenstein, M.D., 2235 Castillo, Santa Barbara.

March 12—**Cancer: Childhood and Adult Tumors.** UCSF at Childrens Hospital, San Francisco. Saturday.

March 12—**Obstetrics and Gynecology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

March 12-13—**Neuropsychiatry in Daily Practice.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

March 13-17—**Alumni Postgraduate Convention, LLU.** Mar. 13-14 (Sunday-Monday)—Refresher Courses. White Memorial Medical Center. Mar. 15-17 (Tuesday-Thursday)—Scientific Assembly. Ambassador Hotel, Los Angeles. Contact: Samuel H. Fritz, M.D., general chairman, 1832 E. Michigan Avenue, Los Angeles 90033.

March 16—**Annual Postgraduate Symposium on Heart Disease.** O'Connor Hospital, San Jose. Wednesday. $15., incl. lunch. Contact: William G. Allayaud, executive director, Santa Clara County Heart Association, 1961 The Alameda, San Jose 95126.

March 16—**Symposium on Obesity.** USC. Wednesday.

March 19—**Catecholamines and Adrenergic Blocking Agents.** Sponsored by the American College of Cardiology and USC. Ambassador Hotel, Los Angeles. Saturday. Members: $30., Non-Members: $40. Contact: Robert W. Oblath, M.D., director, 4911 Van Nuys Blvd., Sherman Oaks.

March 19—**Rheumatic Diseases.** Pres. Med. Ctr. Saturday. 8 hours. $30.

March 19-20—**California Radiological Society Annual Meeting.** Biltmore Hotel, Los Angeles. Saturday-Sunday. Contact: L. H. Garland, M.D., 450 Sutter Street, San Francisco.

March 20-23—**CALIFORNIA MEDICAL ASSOCIATION 95th Annual Session.** Scientific theme: "CURRENT CONCEPTS IN THERAPY: Coronary Artery Disease. Gastrointestinal Hemorrhage. Renal Failure." Biltmore Hotel, Los Angeles. Sunday-Wednesday. Contact: Mr. John Hunton, executive secretary, 693 Sutter Street, San Francisco 94102.

March 25-27—**Postgraduate Assembly in Anesthesiology.** Sponsored by the Anesthesia Section, Los Angeles County Medical Association. International Hotel, Los Angeles. Friday-Sunday. 12 hours. $25. Contact: Thomas W. McIntosh, M.D., secretary, Postgraduate Committee, 686 East Union Street, Pasadena.

March 25-27—**Sex Disorders in Clinical Practice.** UCSF. Friday-Sunday.

March 26—**Endocrinology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

APRIL

April 1-2—**Contrast Media in Abdominal Disease: A Program for the Practicing Physician.** UCSF. Friday-Saturday.

April 1-2—**Joint Manipulations in Perspective.** UCSF. Friday-Saturday.

April 4-8—**Mental Retardation Institute.** USC. Monday-Friday.

April 6-27—**Advanced Funduscopy.** USC. Wednesdays.

April 6-May 11—**Psychiatry in General Practice.** UCSF at Stockton State Hospital, Stockton. Wednesdays.

April 7-June 9—**Ward Walks in Rare Diseases.** USC. Thursdays.

April 12-June 14—**Bedside Cardiology.** USC at St. Vincent's Hospital. Tuesdays.

April 16—**Sports Injuries.** UCLA. Saturday.

April 16-17—**The Uncertain Quest: The Teen-Ager's World.** UCSF. Saturday-Sunday.

April 21-23—**Endocrinology and Metabolism.** UCSF. Thursday-Saturday.

April 23-24—**Neuropsychiatry for the Non-Psychiatric Physician in General Practice.** UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday.

April 25-27—**Annual Meeting of the Council on Medical Television.** UCSF. Monday-Wednesday. Contact: Irving Merrill, M.D., director, Office of Television Research, UCSF.

April 28-29—**General Surgery.** UCSF. Thursday-Friday.

April 28-29—**Symposium on Hypertension.** USC. Thursday-Friday.

MAY

May 5-7—**Ear, Nose, Throat.** UCSF. Thursday-Saturday.

May 5-26—**Neuropsychiatric Management in Daily Practice.** UCSF at Modesto State Hospital, Modesto. Thursdays.

May 6-7—**Obesity.** UCSF. Friday-Saturday.

May 7—**Ventura County General Hospital Annual Staff Seminar.** Ventura County General Hospital. Saturday. 6 hours. No fee. Contact: G. K. Ridge, M.D., V.C.G.H., 3291 Loma Vista Road, Ventura.

May 7-8—**Dynamic Measurements with Radioisotope Techniques for Evaluating Organ Function and Circulation.** UCLA. Saturday-Sunday.

May 12-15—**Hawaii Medical Association Annual Meeting.** Arthritis and Psychiatry. Princess Kailuani Hotel, Honolulu. Thursday-Sunday. 15 hours. $35. Contact: Miss Lee McCaslin, executive secretary, 510 S. Beretania, Honolulu, Hawaii 96813.

May 13—**The Modern Cardiovascular Practitioner.** UCSF at Redwood Empire Heart Association, Santa Rosa. Friday.

May 13-14—**Convulsive Disorders.** UCSF. Friday-Saturday.

May 14—**Humboldt-Del Norte Medical Society Annual Medical Symposium:** "Frontiers in Medicine." Eureka Inn, Eureka. Saturday. 4 hours. Contact: Stanwood S. Schmidt, M.D., president, 707 K St., Eureka.

May 21-22—**Health of the School Child.** UCSF. Saturday-Sunday.

May 23-25—**American Thoracic Society Annual Meeting.** Hilton Hotel, San Francisco. Monday-Wednesday. Contact: James Kieran, M.D., chairman, Medical Sessions Committee, American Thoracic Society, 1790 Broadway, New York, N.Y. 10019.

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TO HAVE YOUR MEETING OR PROGRAM LISTED IN CALIFORNIA MEDICINE

FILL OUT AND MAIL THIS BLANK TO THE ADDRESS GIVEN

(COPY MUST BE **RECEIVED** NOT LATER THAN THE **FIFTH OF THE MONTH PRECEDING** ISSUE)

Continuing Medical Education, California Medical Association
693 Sutter Street, San Francisco, California 94102

Name of Organization____________________

Meeting or Program____________________

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Date____________________Time____________________

Place____________________Fee, If Any____________________

Contact for Information:____________________
(give name, title, address)

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The Physician's BOOKSHELF

STUDIES IN THE PATHOLOGY OF RADIATION DISEASE—N. A. Krayevskii. Translated by A. Lieberman. English Translation Edited by Hermann Lisco and Malcolm Walker. A Pergamon Press Book, distributed by The Macmillan Company, New York, 1965. 219 pages, $15.00.

This monograph by Professor H. A. Krayevskii and his coworkers represents the first English translation of the original volume "Ocherki patologicheskai anatomii luchevoi bolezni" which was published in Moscow in 1957.

Professor Krayevskii is one of the leading pathologists of the Soviet Union. He has presented a great deal of his own work and that of his coworkers on the pathological effects of ionizing radiations from external and internal sources in experimental animals. The author considers dogs as the most suitable animals for experimental investigation of radiation disease and the studies and findings were based largely on the pathological changes which took place in these animals. Only the main pathological features of the disease are presented in this monograph. The radiosensitivity of cells in tissue cultures is not discussed.

The monograph contains ten chapters each of which has been written by a leading Russian authority. Although the purpose of this publication is to present Soviet studies on the pathology of radiation disease, many references are made to data obtained from studies in Japan made on individuals who were exposed to ionizing radiation and also to studies made by Americans. There are 290 references in the bibliography.

The following statement is made in the conclusion: "The study of radiation disease in all its aspects is only just beginning. Two related tasks of great complexity and vital importance before us: the study of the mechanisms by which radiation disease develops and the establishment of a basis for the therapy and prophylaxis of this new disease."

This publication will be of interest to scientists specializing in this field who wish to know how the Soviets are studying the effects of ionizing radiation and what their results have been. Most of the data presented is quite similar to that which has been published by American, English, and other investigators.

JUSTIN J. STEIN, M.D.

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CATARACT OPERATION BY ENZYMATIC ZONULOLYSIS—Doz. Dr. Hans Hofmann, University Eye Clinic, Graz, Austria. Translated by Dorothy Shukri, with a foreword by Professor Karl Hruby. First American Edition translation edited by R. M. Fasanella, M.D. Grune & Stratton, Inc., New York and London, 1965. 118 pages, $6.50. (Paperback.)

This paperback monograph by Dr. Hofmann covers the field of enzymatic zonulolysis completely. The discovery of the zonulolytic process is fascinating in that the medico-legal inhibitory effects on medicine in this country would make a similar discovery highly improbable.

The anatomy and histology of the eyes is reviewed in Chapter 2. The experimental observations of the enzymes and their effects on the different eye tissues are covered in Chapters 3 and 4.

In other chapters the effect of temperature, pH, time and concentration on zonulolysis, and stability of the Enzyme Solutions, are covered in detail. Chapters on Enzyme Promoters and Inhibitors, Mechanism of Zonulolysis, Sensitization, and effect of Enzymes on Suture Material complete the preclinical material.

The second section of the monograph deals with the clinical application of Zonulolysis. In reviewing the literature and adding his own comments, Dr. Hofmann presents a number of conflicting statements. This is not entirely his fault, since the literature is in itself a mass of conflicting statements.

In summary, Dr. Hofmann proposes that trypsin is a far more safe drug than alpha-chymotrypsin and is to be preferred for clinical use.

ROBERT M. SINSKEY, M.D.

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CARDIOMYOPATHIES—Ciba Foundation Symposium—Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., F.R.C.P., and Maeve O'Conner, B.A. Little, Brown and Company, Boston, 1964. 428 pages, $12.50.

This monograph contains the proceedings of a recent symposium held in London, in which a few leading authorities presented formal papers and exchanged ideas in informal discussions. The title of the symposium is somewhat misleading: rather than "cardiomyopathies" in general, 75 per cent of the meeting was devoted to one special type of it: obstructive cardiomyopathy or "Hypertrophic muscular subaortic stenosis." Only the last few presentations deal with other forms: fibroelastosis, Friedreich disease and viral myocarditis.

The main subject is covered in depth. Basic anatomy and physiology of obstructive cardiomyopathy is followed by clinical features, pharmacology and surgical treatment. Individual presentations are good, even though most of them are not new: the very reason for inviting a given speaker is based on previous published work by him, so that repetition is unavoidable. However, most speakers have taken the trouble of adding new material and broadening their presentations, rather than restating previously published work. However, the highlight of the book is the discussions that follow each group of presentations. Here one can find pertinent criticisms, reinterpretation of the lecturers' material, exchange of views and provocative ideas, which might be unsuitable for formal presentations.

The combination of authoritative chapters and informal discussion makes this an excellent monograph which is highly recommended to those interested in cardiac disease even though the subject is a relatively common clinical syndrome, one which the average practicing physician is likely to encounter.

A. SELZER

MULTIPLE SCLEROSIS—A Reappraisal—Douglas McAlpine, M.D.(Glasg.), F.R.C.P., Emeritus Consultant to the Middlesex Hospital; Honorary Consultant Physician to Maida Vale Hospital; Charles E. Lumsden, M.D. (Aberd.), F. C. Path., Professor of Pathology, University of Leeds; Late Sir Henry Head Research Fellow of the Royal Society and Rockefeller Traveling Research Fellow in Medicine, Columbia University, New York; and E. D. Acheson, M.A., D.M.(Oxon.), M.R.C.P., First Assistant Nuffield Department of Clinical Medicine, University of Oxford; Medical Director Oxford Record Linkage Study. The Williams and Wilkins Company, Baltimore, Md., 165. 415 pages, $10.75.

This monograph is presented in three parts. Part 1 is brief, a total of 34 pages dealing with the epidemiology of multiple sclerosis (M.S.). The next part of 170 pages is primarily a division of the previous monograph on M.S. by Dr. McAlpine and presents the clinical aspects of this disorder, including the natural history, early signs and symptoms, diagnostic criteria, course and prognosis and treatment. The remaining part deals with the clinical pathology of multiple sclerosis exhaustively discussing cerebrospinal fluid, cytology and proteins, amino acid, carbohydrate metabolism and enzymes in M.S. and the chemical pathology of lipids in demyelinating disease, with a final chapter in which the question of multiple sclerosis as an immunological disorder is examined and presented. This last part does not, in fact, deal in any way with the pathology and pathogenesis of multiple sclerosis. This new major part concerned with clinical pathology is the important addition to the old monograph. It reviews the vast literature on M.S. and states and analyzes the current concepts and modes of approach to the fundamental pathogenesis of this disorder.

As the book is essentially in two parts, one clinical and the other laboratory, it has appeal to both the clinician and the laboratory and research worker in M.S. It is also an important reference text. Thus, while one worker may be interested in the observation that critical flicker fusion frequency may be lower in pallor of the optic nerves, and another in the probable site of production of antibodies in M.S., the practicing physician may have an interest in the probability whether a patient suspected of multiple sclerosis, who has 40 or 50 cells in his CSF or a protein of over 120 mg, has multiple sclerosis. Equally, the treating physician may find here the answer to such questions as what is the effect of trauma on multiple sclerosis, what is the place of ACTH in the treatment of acute attacks, and what is the value and method of intrathecal phenol for spasticity? It should be noted that like most monographs, the subject index may be lacking, and this is so here. Thus, one cannot find phenol in the subject index, although it is dealt with comprehensively in the text.

This is indeed an excellent, careful presentation of major importance and interest to physicians and laboratory workers.

Donald MacRae, M.D.

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ENGLISH MEDICAL HUMANISTS, THOMAS LINACRE AND JOHN CAIUS—Logan Clendening Lectures on the History and Philosophy of Medicine: Twelfth Series—C.D. O'Malley. The University of Kansas Press, Lawrence, Kansas, 1965. 54 pages, $2.00.

For many years the anual lecturer has paid tribute to the late Dr. Logan Clendening, a generous physician whose scholarly spirit has done much to foster the humanities and the history of medicine at the University of Kansas. The present essayist, Professor of the History of Medicine at the University of California, Los Angeles, has chosen as his topic for the occasion, the development of medical humanism in England. This he has done by presenting two brief sketches on the life and work of the well-known medical humanists, Thomas Linacre (c. 1460-1524) and John Caius (or Keys) (1510-1573), presumptively since they represent the beginning and the end of an era.

The essayist gives a straight-forward and easily readable, if somewhat pedestrian, account of the known facts concerning Linacre and Caius and their contributions to the revival of classical medicine, notably Galenism, through improved translations from the Greek texts.

The humanistic movement had its origins in Italy during the late fourteenth and early fifteenth centuries. It was essentially a literary movement initiated by the enthusiasms engendered by the re-discovery of the ancient manuscripts and especially for the study of Greek aroused by Manuel Choysoloras (c. 1350-1445), called 'litterarum Graecarum restituor,' and Theodorus Gaza (c. 1398-1478). The humanistic movement invaded medicine comparatively late during the latter part of the fifteenth and first half of the sixteenth century. The movement sought a return to classical ideals and form and was, in essence, a reactionary movement. In its application to medicine it did much to clear away the accrued dross of mediaevalism and further, set the stage for the future. However, owing to its over-emphasis on Galen and Hippocrates and its literary nature, the humanistic movement was highly restrictive to the development of the physician, as distinct from the surgeon, by destroying his scientific objectivity.

In England humanism had its initial center at Oxford through the efforts of Latimer, Linacre, Grocyn, More and Colet, to pass much later, at the end of the first-quarter of the sixteenth century, to Cambridge. At Cambridge the College of St. John, under the guidance of its master, Nicholas Metcalfe, became celebrated as the seat of the new learning and of great influence upon the intellectual life of that university's graduates such as John Caius. The selection by the author of Linacre and Caius as representative of English medical humanism was an obvious choice since they were the only major figures in the movement. This choice should have provided the author with an opportunity of contrasting and comparing the distinctive traditions of Oxford and Cambridge in English medicine and their influence on Linacre and Caius.

In addition, the author has failed to examine the important relationship and contrasts between the graduates of the universities and the membership of the powerful medical guilds. Thus the volume at hand disappointingly lacks substance except for its brief biographical content on the lives of two notable physicians.

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COMPARATIVE HEMATOLOGY—Warren Andrew, M.D,. Ph.D., Chairman, Department of Anatomy, Indiana University School of Medicine, Indianapolis, Indiana. Grune & Stratton, New York, 1965. 188 pages, $22.75.

This book is a comprehensive summing up, stressing morphology of what is known about the blood of invertebrates, fishes, amphibians, reptiles, birds and mammals. Excellent illustrations, including a color atlas section and electron micrographs, appear throughout the book. Many details about blood counts for the various species are given. The book contains many intriguing bits of information, e.g.—Red cell life span in the turtle is about 2 years, bats have red cell count of over 10,000,000, and decreased erythropoiesis in winter; horses show a difference in red cell counts between the sexes, stallions' counts being 40 per cent higher than mares; camels have ovalocytes; the sickle cells in the deer are not associated with hematologic abnormality or disease.

The material is rather far removed from current areas of interest and investigation in hematology, but it is a useful reference for hematologists of catholic interest.

R. O. Wallerstein, M.D.

DEVELOPMENTAL ANATOMY—A Textbook and Laboratory Manual of Embryology—Seventh Edition, Leslie Brainerd Arey, Ph.D., Sc.D., LL.D., Robert Laughlin Rea Professor of Anatomy, Emeritus, Northwestern University; W. B. Saunders Company, Philadelphia and London, 1965. 695 pages, $10.00.

This old and well-respected text has reached its seventh edition, the previous edition having appeared in 1954. The book is beautifully published. Almost seven hundred illustrations, many of them in color, are of excellent quality and clarity. There are three major sections—one on general development, one on special development, and finally a laboratory manual of embryology. The latter is one hundred pages long and is devoted to the chick and pig embryos. The first section deals with fundamental concepts—growth, oogenesis, spermatogenesis, meiosis, ovulation, embryonic and fetal stages, the fetal membranes, and placentation. Chapters on experimental teratology and embryology are included. This section has been brought up to date in many ways—the number of human chromosomes has been corrected, brief reference is made to the role of DNA and RNA and some other new information has been included. However, most of the references are to older publications, and even the latest do not seem to go beyond the year 1962. Somehow the excitement of modern molecular biology and cytogenetics is missing. The second section is devoted to specific details of tissue, organ and organ system development. There does not appear to be a great deal of revision from the previous edition but once again inaccuracies have been corrected and some new references have been added.

This remains a valuable textbook of embryology and will be useful to physicians and medical students who wish to refresh their knowledge of this important basic science.

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THE FEAR OF BEING A WOMAN—A Theory of Maternal Destructiveness—Joseph C. Rheingold, M.D., Ph.D., Research Associate in Psychiatry, Harvard Medical School. Grune & Stratton, Inc., New York and London, 1964. 756 pages, $10.00.

In an interesting preface the author states that the book is the report of ". . . an epistemologic experiment." In this he attempted to hold in abeyance ". . . the knowledge and practices acquired by training and to allow observation to take original form in a merging-of-consciousness psychotherapeutic procedure." As he continued, over a period of twelve years, he perceived that early maternal influence was a preeminent factor of determination.

This large book is divided into three parts. The first part deals with The Mother, the second with The Child and the third is a discussion of Treatment and Prevention. In part one the author presents a detailed discussion of the subject of maternal destructiveness including evidence that hatred and hostility are common in the mother-child relationship. He puts special emphasis on the mother-daughter relationship.

The second section is the longest part of the book; about two-thirds of the total, and this reviewer finds it impossible to summarize. It includes chapters on The Fear of Being a Woman and Personality Development, Menstruation and Its Disorders, Sexual Frigidity, and The Mother-Fetus Relationship among others.

In the third and final section the author presents material from the psychotherapy of women to support his theory of maternal destructiveness. Also, in this section he gives a resume of the theory. "By maternal destructiveness I mean whatever influence the mother exerts upon the fetus, the newborn, the infant, and the young child to which it is susceptible and which tends to interfere with or distort, or provide inadequate supplies for, wholesome personality development. Such influence may be exerted by other persons (father, siblings, a grandmother, etc.) but given the strong likelihood of prenatal response to maternal emotion and possibly to maternal attitude, and the almost exclusive or preeminently important role of the mother in infant care, it is she who is primarily and preponderantly responsible for unfortunate effects. The infant possesses an extraordinary perceptiveness of its mother's attitudes in relation to its survival. If these attitudes are nurturant, the infant develops a sense of trust in the environment; if they are rejective or vacillating, it acquires a fearfulness that we designate basic anxiety. Anxiety may inhere in the infantile state, but nurturance tends to assuage it, while uncertainty of protection tends to aggravate it. The maternal threat consists of a negative factor of failure to supply the needs of the infant and and active factor of hostility expressing itself in mutilative and annihilative impulses, which give rise to the mutilation and death complexes." He continues and among other points expresses the belief that in the transmission of destructiveness ". . . only the mother-daughter relationship is significant." He ends with a discussion of prevention.

This reviewer found the book exceedingly difficult to read and must admit that he has not read it all the way through. The subject matter is most important and deserves careful study but this presentation seems unduly cumbersome. Some of the author's attitudes suggest strong bias, for example in discussing the infanticidal impulse during parturition and the lying-in period he reflects, at the delivery table, on ". . . the nine long months of anxiety, discomfort and complications. . . ." He makes no reference, at least not a close one, to the fact that for many women the elements of anxiety, discomfort and complications may be minimal and that the period of pregnancy may well be one of great pleasure and well-being.

The reader who has a great deal of time and who is well supplied with interest in the subject will find this book rewarding. Parts of it most certainly should be presented to the lay public as well as to the professional groups.

CHARLES W. TIDD, M.D.

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OUTLINE OF ENDOCRINE GLAND SYNDROMES—T. S. Danowski, B.A., M.D., Professor of Medicine, University of Pittsburgh School of Medicine; Senior Staff Physician at the Children's Presbyterian-University, Magee-Womens, and Shadyside Hospitals; Consultant in Metabolism, Oakland and Butler Veterans Administration Hospitals. The Williams & Wilkins Company, Baltimore, Md., 1965. 374 pages, $5.75 (Paperback).

This small handbook of some 374 pages, entitled "Outline of Endocrine Gland Syndromes" should be more properly called "Synopsis of Endocrine Disorders" since it covers far more than the usual endocrine syndromes encountered. It starts with a chapter on the endocrinopathy with non-endocrine gland cancers and then systematically reviews the literature of the various glands including some of the syndromes described. Unfortunately, it omits the hormonal secretions of the pancreas, since this is covered by a volume that the author has edited for the American Diabetes Association. However, this does not entirely make up for the lack of the syndromes associated with disorders of pancreatic function and especially with hypoglycemic disorders, which perhaps should be included in future editions of this book.

I found the volume extremely valuable for the review of the classical and also recent literature with excellent references to each chapter. The text itself is rather brief and while it enumerates the syndromes and associated disorders, it perhaps does not place ample emphasis on what is more common and what is less common, or extremely rare. It would therefore not be an ideal book for the medical student, but would be best suited for the advanced student of endocrinology for whom it would serve as a ready reference guide. On many occasions the author refers to his own larger volumes 1, 2, 3 and 4 of Clinical Endocrinology, a monumental work published in 1962, to which this small outline really is a companion volume. If one must take exception to the practicality of this book, it is perhaps due to the rather arbitrary division into various chapters in each part, that is, syndromes of hyper-and hypofunction are rather intermixed, and many chapters refer to medical or surgical procedures rather than to syndromes. A more integrated type of classification in each part would be of great help in organizing a review of an endocrine gland. There are a number of minor errors in cross-reference to certain chapters; for instance on page 131. There are also some broad statements; for instance page 134, "hypercalcemia tends to be more marked in patients with hyperparathyroidism and diffuse hyperplasia than due to adenoma"; and such statements as on page 181, "it is estimated that osteoporosis has occurred in virtually all women past the age of 65 and almost all men" which is certainly not in accord with current evidence. In Chapter 47 on Urinary Calculi, the recent work of Howard and others on the phosphate treatment and its effect on calcifying properties of urines of stone formers is omitted. On page 200 it states "hypophosphatemia occurs in Lignac-Fanconi syndrome with cystinuria *and* cystine renal calculi" with which this reviewer does not agree. He also does not agree with the statement on page 243, "doses of cortisone no smaller than 500 mg/day should be used in adrenalectomy." Part 10 of the volume contains differential diagnosis of endocrinopathy and miscellaneous syndromes. Some of these are really not endocrine syndromes and perhaps are best integrated into the text under the various chapters.

In spite of these minor criticisms, this book is extremely valuable for a person attempting to review the classical and also the most recent literature on most endocrine gland disorders. It is especially valuable in the preparation of case reports, since it covers not only the American but also the foreign literature in great detail. It is inexpensive and since it is in soft covers, it will probably be revised quite frequently and brought up to date. It is hoped that the author will enhance the usefulness of this volume by better integration of the various chapters in each section.

FELIX O. KOLB, M.D.

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HANDBOOK OF PHARMACOLOGY—The Actions and Uses of Drugs—Second Edition, Windsor C. Cutting, M.D., Director, Pacific Biomedical Research Center, and Professor of Pharmacology, University of Hawaii; Editor, Annual Review of Pharmacology; Chairman, USAN Council; formerly, Professor of Experimental Therapeutics, Stanford University School of Medicine. Appleton-Century-Crofts, Division of Meredith Publishing Company, New York, 1964. 647 pages, $5.95 (Paperback).

This handbook is written in the hope "that the brief presentation will prove of orienting value to students, a uesful supplement to the large texts, and a means of quick summary for the practicing physician." The book is divided into four parts: an introduction describing the principles of drug action, drugs acting on foreign invaders and cancer, drugs acting on somatic systems (heart and other muscles, blood, etc.) and drugs acting on the nervous system. There are 61 chapters and an index. Each chapter is written in outline form with the subheadings History, Chemistry, Actions, Mechanism, Pharmacology, Toxicity, Uses, Preparations. Almost every useful drug is included and most of them are described sufficiently to permit an intelligent selection of a particular drug or derivative for each indication. Dr. Cutting has not written a textbook, but rather a book for quick reference and review. This first revision of the authors First Edition is as up-to-date as is possible for a book of this character, not only in the inclusion of the newest drugs, approved for use at the time of writing, but in a description of the known chemical mechanisms involved in drug action. The single-plane structural formula of almost every drug is shown and this takes up at least 10 per cent of the space. For the practicing physician these formulas probably have little interest, and the student will find most of them in the larger, more detailed textbooks he studies for his course in pharmacology but for the pharmaceutical chemist and research pharmacologist they afford an orientation in chemical pharmacology. For the physician, the use of both the non-proprietary name and the trade-marked name are helpful.

The author has succeeded in accomplishing his purpose in preparing a book for quick review for the student and physician, and has done more in that the research scientist, especially in the pharmaceutical industry, will have frequent occasion to turn to the book for orientation.

While preparing this review, the reviewer learned of the appointment of Dr. Cutting as Dean of the new School of Medicine of the University of Hawaii.

CLINTON H. THIENES, M.D.

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PHYSIOLOGIC PRINCIPLES OF SURGERY—Second Edition—edited by Leo M. Zimmerman, M.D., Professor of Surgery Chicago Medical School; Senior Attending Surgeon, Michael Reese Hospital; and Rachmiel Levine, M.D., Chairman, Department of Medicine, New York Medical College. W. B. Saunders Company, Philadelphia, 1964. 858 pages, $20.00.

It has been estimated that in the sciences, 50 per cent of the information which is taught today will be either outmoded or subject to considerable revision ten years hence. Certainly rapid advances have been made in physiology during the past decade, and to keep the medical practitioner current in these changes presents a major challenge to medical educators. It is unrealistic to expect a physician in practice to find the time or energy to read a standard medical school text in physiology. If, however, the text contains mainly information pertinent to his specialty and eminently useful in its practical application, it should represent a considerable incentive for the clinician to read and absorb its contents.

Among the many recent physiology texts directed toward the practicing physician, Leo Zimmerman and Rachmiel Levine's "Physiological Principles of Surgery" is one of the outstanding efforts. Directed toward the surgeon, it is a compendium of subjects which is of interest not only to the general surgeon but to the subspecialist as well. Each chapter is written by an acknowledged expert in his field, and a very broad diversity of subjects is covered in thirty-seven chapters.

The excellence of coverage for any subject of necessity falls upon the individual author. Occasionally, as for example the chapter on the "Breast," the writer's style is distracting. In certain chapters, notably "Congenital Heart Disease," the subject is treated so thoroughly as to be considered a monograph in itself. A chapter on "Blood Transfusion" might well have been shortened by omitting a dissertation on blood bank procedures. On the other hand, occasionally more information of a clinical type would have been desirable, as in the chemotherapy of cancer in "Some Physiologic Aspects of Neoplastic Diseases."

The opening chapters in the text deal with general problems, such as the response of the body to injury, infection, and operation, and the reviewer feels that there is a certain redundancy in the coverage. Kinney and Moore's superb chapter on "Surgical Metabolism in Metabolism of Body Fluids" has been taken directly from Bland's recent text on "Clinical Metabolism of Body Water and Electrolytes," and had it been expanded a bit, two chapters, "The Metabolic Response to Injury" and "Nutrition in Surgery" could have been omitted.

Chapters of particular interest to the general surgeon are very well done on the gastro-intestinal tract, the liver, biliary tract, pancreas and endocrine glands. The normal and abnormal physiology of these organs, along with the meaning and significance of the seeming myriads of new clinical tests available are for the most clearly described.

The editors have been careful to include chapters of interest in the subspecialties as well. Thomas Baffes "Surgery of the Newborn" is excellently written. Six or seven chapters are devoted to the lungs and cardiovascular surgery. The kidneys, lower urinary tract, and male genital tract each have a separate chapter. Alex Tulsky has contributed a chapter on "The Uterus and Ovaries," and the final chapter is devoted to the central nervous system. Rather surprisingly, there is no chapter on bone and joint physiology for the orthopedist, though a physical medicine chapter is included in the biomechanics of the peripheral motor system.

Two chapters on pain and anesthesiology are covered in the text, and certain specialized topics like "Transplantation of Tissue," "Plasma Proteins," and "The Blood and Blood Forming Organs" in which many outstanding recent advances have been made are presented in a most lucid series of chapters.

The authors in the text are all authorities on their respective subjects, and it is to their credit that each subject has been treated quite objectively, for the most part, with little intrusion of personal bias. Rarely are statements made which contradict those presented in other chapters, and one is never left with the feeling that an entire subject has been presented arbitrarily. The second edition of "Physiologic Principles of Surgery" should make a valuable edition to a surgeon's library.

FREDRICK W. MARX, JR., M.D.

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NARCOTICS—Edited by Daniel M. Wilner, Ph.D., Professor of Public Health, and Gene G. Kasselbaum, Ph.D., Associate Research Sociologist, both School of Public Health, University of California, Los Angeles. McGraw-Hill Book Company (Blakiston Division), New York, 1965. 302 pages, $3.50.

The book represents a compilation of papers presented at a National narcotics conference at U.C.L.A. in April 1963.

Numerous knowledgeable individuals present various facets of the problem including a report on the rehabilitation program in California.

This represents one of the largest programs to date and results so far justify cautious optimism. Many of the authors of the papers presented similar material at the White House Conference, and one is certainly unimpressed with the infallibility of experts.

The same evidence may be used to draw astonishingly divergent conclusions. One is somewhat bewildered by the inability to differentiate between the treatment and perpetuation of addiction. A report of research on efforts to produce a pain-relieving drug which is not also euphoric is somewhat encouraging.

For those who view addiction with equanimity and are preoccupied with the merits of the English system, the Hong Kong article is of interest.

Approximately one out of every eight adult males in Hong Kong is a drug addict. It is unfortunate that this ideal situation for research in the problem is not utilized with funds from the United Nations or World Health Organization.

The problem in the United States while serious enough to the friends and relatives and to the addict himself is relatively minor compared to the problem of alcoholism.

In summary it should be pointed out that the Editors are not promoting any particular gospel of their own, but have presented current thinking by knowledgeable people on this serious problem.

WM. F. QUINN, M.D.

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PHYSIOLOGY OF BLOOD PLATELETS—Recent Biochemical, Morphologic and Clinical Research—Aaron J. Marcus, M.D., Chief, Hematology Section, New York Veterans Administration Hospital; Assistant Professor of Medicine, Cornell University Medical College; Associate Visiting Physician, Second (Cornell) Medical Division, Bellevue Hospital; and Marjorie B. Zucker, Ph.D., Senior Research Associate, American National Red Cross Research Laboratory (Eastern Division); Associate Professor of Pathology, New York University School of Medicine. Grune & Stratton, Inc., New York, 1965. 162 pages, $7.00.

This text of this small volume on blood platelets occupies only 100 pages. The variable and contradictory reports on this elusive cellular particle are listed with relatively little attempt by the authors to apply value judgments or superimpose their own interpretations. The book is thus too confusing to be recommended as a quick review for readers with limited knowledge of the platelet literature.

On the other hand, it contains a remarkably up-to-date and inclusive bibliography of 44 pages, referring to English, French and German publications, which provides an invaluable starting point for a serious literature search into any aspect of the subject of platelets.

The areas covered include the biochemistry and electron microscopic anatomy of platelets; platelet factors involved in coagulation; aggregation, adhesion, clot retraction, viscous metamorphosis and hemostatic plug formation; thrombocytopathia, thrombasthenia, thrombocythemia and von Willebrand's disease; and thrombopoiesis, platelet survival and platelet transfusions.

This book belongs in every hematology reference library.

HERBERT A. PERKINS, M.D.

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PAIN IN THE CHEST—William H. Wehrmacher, M.D., F.A.C.P., F.A.C.C., Northwestern University Medical School, Passavant Memorial Hospital, U.S. Veterans Administration Research Hospital, Chicago, Illinois. Charles C Thomas, Publisher, Springfield, Ill., 1964. 403 pages, $14.00.

This book is an excellent detailed review of many of the obscure, as well as the common, causes of chest pain. There is very little new information, but it does provide a convenient summary of a large volume of useful information on this important subject. The author emphasizes the importance of etiologic diagnosis and not just the simple determination of whether or not chest pain is due to coronary artery disease. There is considerable emphasis on the historical aspects of each entity, as well as a fine bibliography at the end of each chapter.

This volume is too verbose for medical students but should prove to be a very useful reference text for internists and general practitioners.

VARNER J. JOHNS, JR., M.D.

RADIOLOGIC STUDIES OF THE GRAVID UTERUS—Paul A. Bishop, M.D., Consulting Radiologist, Pennsylvania Hospital; formerly, Director of the Department of Radiology, Pennsylvania Hospital, and Chief of Radiology of its Benjamin Franklin Clinic; Professor of Radiology, School of Medicine, and Professor of Radiology, Graduate School of Medicine, University of Pennsylvania, Philadelphia. Foreword by Robert A. Kimbrough, M.D., with 250 illustrations. 279 pages, $14.50.

This is a neat and well illustrated monograph which well fulfills the title. The section on "Hazards and control of radiation exposure" might be classified as optimistic. The work should be of interest to radiologists and obstetricians practicing in lying-in hospitals.

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OPHTHALMOLOGY—Principles and Concepts—Frank W. Newell, M.D., M.Sc. (Ophth.), F.A.C.S., Professor and Head, Section of Ophthalmology, The University of Chicago. The C. V. Mosby Company, St. Louis, Mo., 1965. 491 pages, $12.25.

This initial edition of a textbook for undergraduate and graduate students will certainly become one of the most widely recommended texts for this group of readers.

Almost all aspects of ophthalmology are discussed in a very readable and succinct manner.

Especially noteworthy is the excellent index which will allow the student direct reference to his topic of interest.

There are many classification charts and outlines which give an excellent bird's eye view of the organizational structure of the topic being discussed. The photographs are superb.

This text may be highly recommended for students of ophthalmology and as ready reference book for general practitioners.

ARTHUR JAMPOLSKY, M.D.

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PHARMACOLOGY OF CHOLINERGIC AND ADRENERGIC TRANSMISSION—Proceedings of the Second International Pharmacological Meeting, Prague, August 20-23, 1963—Edited by G. B. Koelle, Department of Pharmacology, University of Pennsylvania, Philadelphia, Pa.; W. W. Douglas, Department of Pharmacology, Albert Einstein College of Medicine, New York, N.Y.; and A. Carlsson, Department of Pharmacology, University of Göteborg. V. Trcka, Research Institute of Pharmacy and Biochemistry, Prague, Assistant Editor. A Pergamon Press Book, distributed by The Macmillan Company, New York, 1965. 346 pages, $15.00. (The Proceedings are published in a set of 11 volumes—this is number 3.)

The subject matter for this volume consists of a series of reports by investigators generally acknowledged as major workers in this field. These written reports are "bare bones" abstracts of the investigative procedures, yet sufficiently fleshed out to substantiate the conclusions which are reached.

Papers selected for inclusion in this volume are arranged in sequence, leading from such basic concepts as the role of sodium ions in the release of acetylcholine, through the possible mechanisms of acetylcholine action in muscle, and including the possibilities for therapeutic application. Papers dealing with adrenergic transmission also follow the same logical sequence, beginning with the localization of neuronal monoamines at the cellular level, through drugs which interfere with storage and release of adrenergic transmitters and concludes with the functional significance of noradrenaline depletion by metaraminol and dextro-adrenaline.

It is difficult to select any one or two of the participants as being superior to others, but particular commendation should be given to W. W. Douglas for his paper on acetylcholine as a secretogogue. This aspect of acetylcholine action has not been extensively investigated, probably because of the many technical problems involved, but the paper represents a significant elucidation of those factors responsible for formation of a glandular secretion and, by inference, those factors leading to formation of neurohormonal agents themselves. The other paper selected by this reviewer as an example of exceptionally lucid writing is that of J. Axelrod, entitled "Metabolism and Inactivation of Noradrenaline and Adrenaline and the Effects of Drugs." Dr. Axelrod shows a clear progression of experiments leading to a series of conclusions, as beautifully arranged in their way as the sequences developed in the exploits of a popular fictional detective. Persons whose primary areas of responsibility are in physiology, pharmacology, biochemistry and psychology will find this volume valuable. In addition, physicians who are interested in the deeper implications of therapeutic agents will be delighted with the references to drugs in current therapeutic usage. Students desiring a grasp of these areas will find the book a valuable resource and all who peruse it will enjoy the entirely logical progression and intermingling of theory and fact.

ROBERT W. EARLE, Ph.D.

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THE ROENTGEN DIAGNOSIS OF TRAUMA—Herbert R. Zatzkin, M.D., F.A.C.R., Chairman, Department of Radiology, Meadowbrook Hospital, the Nassau County Public General Hospital, East Meadow, Long Island, New York; Consultant Radiologist, Community Hospital, Glen Cove, New York; Consultant Radiologist, Hempstead General Hospital, Hempstead, New York; Consultant Radiologist to the Office of the Medical Examiner, Nassau County, New York. Year Book Medical Publishers, Inc., 35 E. Wacker Drive, Chicago, Ill., 1965. 448 pages, $22.00.

This monograph is divided into 14 sections dealing respectively with the x-ray signs of trauma in various tissues, and with the specific findings in head, neck, thorax and so forth. The illustrations are reproduced to simulate the original roentgenograms, and are mostly of very good quality. There are references at the end of each chapter and an adequate index.

The work could be recommended were it not for the section dealing with injuries to the neck. In this section the author perpetuates the use of the erroneous term "whiplash" instead of the term "sprain" now recommended by the originator of the former word. Furthermore, he proceeds to mention a series of symptoms ranging from aching in the eyeballs to diffuse emotional tension attributable to such neck sprains. Nowhere is Macrae's dictum reproduced that "The radiological appearance of the cervical spine of patients with so-called whiplash injury is the same as that of the cervical spine of patients without said injury." Since several miles of sponge rubber and leather are used up each year in the "treatment" of the "subluxations" alleged to occur with cervical sprains, one will hope that subsequent editions will contain suitable amendation.

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TESTICULAR FEMINIZATION—Endocrine Function of Feminizing Testes; Comparison with Normal Testes—Hans H. Simmer, M.D., U.S.P.H.S.-Research Career Development Awardee; Associate Professor of Obstetrics and Gynecology; Head of the Endocrine Laboratory, University of California Medical School, Los Angeles, Calif.; Ronald J. Pion, M.D., Assistant Professor of Obstetrics and Gynecology, University of Washington Medical School, Seattle, Washington; formerly, U.S.P.H.S.-Trainee in Reproductive Physiology, University of California Medical School, Los Angeles, Calif.; and William J. Dignam, M.D., Associate Professor of Obstetrics and Gynecology, University of California Medical School, Los Angeles, Calif. Charles C Thomas, Publisher, Springfield, Ill., 1965. 108 pages, $6.00.

This delightful book covers in great detail the rather rare endocrine syndrome of testicular feminization. As a matter of fact, it only covers a more common form of this disorder associated with lack of virilizing features. While this rare syndrome would not be ordinarily of interest to the general practitioner or general internist, a careful review by the authors of the normal physiology and secretory physiology of the human testis is of great value since it is critically reviewed. It is then compared with the abnormalities encountered in this rare syndrome of testicular feminization. In the last part the authors then summarize the current thought of how it is possible in this syndrome to have normally functioning testes, yet not to show evidence of androgenic, but rather evidence of estrogenic activity. They postulate end-organ insensitivity. The possibility that co-factors are missing or that antagonists are present to the action of testosterone are not entirely ruled-out, nor is the exact reason why these patients have adequate breast development. It is of interest that the authors are from the Department of Obstetrics and Gynecology and yet have studied in great detail testosterone and estrogen secretion of the human testis. They have perhaps wisely omitted the somewhat depressing recent finding by Dorfman and his group that testosterone secretion decreases with advancing age. Also, as proud Californians, we would like to consider this syndrome as the Goldberg-Maxwell syndrome, since these authors have called attention to this interesting syndrome in 1948.

The book is highly recommended for endocrinologists and for others interested in the endocrine function of the normal and abnormal testis.

Felix O. Kolb, M. D.

* * *

FROM AUSCULTATION TO PHONOCARDIOGRAPHY—Aldo A. Luisada, M.D., Professor of Medicine and Professor of Cardiovascular Research, The Chicago Medical School; Attending in Medicine and Director of the Division of Cardiology, Mount Sinai Hospital of Chicago. With the collaboration of D. M. MacCanon, Ph.D.; L. M. Rosa, M.D.; P. M. Shah, M.D.; and R. Zalter, M.D. The C. V. Mosby Company, St. Louis, Mo., 1965. 351 pages, $17.75.

This book is an outgrowth of the author's long and productive interest in phonocardiography and cardiac auscultation. It is by far the most up to date exposition of the general subject of phonocardiography in print. The results of recently developed techniques are used freely throughout the text; these include pharmicodynamic phonocardiographic studies, intracardiac phonocardiography, first (and second) derivatives of pressure waves, and studies on subjects with prosthetic cardiac valves. The copious illustrations are of excellent quality, form an integral part of the authors presentation, and may explain in part the rather high price of the book. Extensive use is made of the apex cardiogram, arterial and venous pulse wave tracings and intracardiac pressures as reference tracings.

While phonocardiography is not covered in an encyclopedic manner, yet this book is much more than just a synopsis of the subject. The large and very current bibliography is in itself a valuable compilation. "Classical" concepts of the production and transmission of cardiac sound are examined and new concepts formulated where experimental data makes this necessary. Some of the author's views on the genesis of the heart sounds are controversial although backed up by impressive experimental evidence.

Cardiologists, internists, teachers of physical diagnosis, and other physicians with a special interest in cardiac sound will find this book a valuable addition to their reference libraries. It will be of particular interest to those actively engaged in recording and interpreting phonocardiograms (about one quarter of the book is devoted to technical aspects).

Rex N. MacAlpin, M.D.

* * *

SURGERY OF THE PAROTID GLAND—Robin Anderson, M.D., F.A.C.S., Head, Department of Plastic Surgery, Cleveland Clinic Foundation, Cleveland, Ohio; and Louis T. Byars, M.D., F.A.C.S., Associate Professor of Clinical Surgery, Department of Plastic Surgery, Washington University School of Medicine, St. Louis, Mo. The C. V. Mosby Company, St. Louis, Mo., 1965. 177 pages, $12.75.

Two well-respected leaders in the field of Plastic Surgery have written an authoritative monograph on Surgery of the Parotid Gland. This 177 page treatise is in hard cover, and is profusely illustrated. Of particular note are some rather unusual orientation photographs relative to dissection of the facial nerve. The pathology, diagnosis, treatment, and discussion of complications and secondary reconstruction show the stamp of authority of these fine and experienced surgeons. It is easily readable and is well indexed and is recommended for purchase by medical students, house officers, and all those concerning themselves with surgery of this important area.

George V. Webster, M.D.

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*Lubowe, I. I.: Scalp dermatoses: Treatment with fluocinolone acetonide in propylene glycol. Skin 3:267 (Sept.) 1964.

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It now takes 24 per cent less of an American factory worker's time on the job than 20 years ago to pay his doctor's bill. This finding is based on information from the U.S. Bureau of Labor Statistics, which regularly compiles figures on the cost of a number of items in terms of work time.

During the past 20 years, the hourly wage of factory workers climbed by 150 per cent. Overall per capita income in the U.S. increased 113 per cent.

In comparison, physicians' fees have increased only 89.8 per cent.

Physicians' fees in that past 20 years, as measured by the Bureau of Labor Statistics' Consumer Price Index, have increased less than the price of movie tickets, men's haircuts, men's suits, auto insurance, shoes, newspaper subscriptions, and even shampoos and wave sets.

In fact, physicians' fees have gone up less than postal charges by the federal government, which have jumped 100.8 per cent in 20 years.

More than $11 billion was spent by Americans in package liquor stores, cocktail lounges, bars and taverns in 1963. This is almost twice as much as Americans paid their doctors.

Americans spent nearly $42 billion in 1963 on recreation, alcohol and tobacco. On health care—including hospitals, doctors, dentists, drugs and all other items—they spent about $23½ billion.

Out of every dollar spent by Americans in 1963, only slightly more than six cents went for medical care. Out of this six cents, only a penny and a half was paid to physicians.

General inflationary trends in the national economy are only partly responsible for the increased amounts spent on health care. Other factors include, for example, the public demand for greater medical specialization, the development and use of improved scientific and technical equipment, and the need for trained medical and paramedical personnel. Higher wages and shorter hours for hospital personnel and increased capital expenditures by hospitals have contributed to increased costs.

What can't be measured, of course, is the improving quality of medical care which the patient receives. Physicians and their allies in the health care field are saving lives now which would have been lost even 20 years ago. The doctor is preventing or limiting more diseases. Years have been added to the life span of the average American.

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New Magazine for Physicians' Wives

A new magazine, *MD's Wife,* is being published by the Women's Auxiliary to the American Medical Association.

Designed especially for physicians' wives, the bimonthly publication features four-color illustrations, national advertising, and a variety of features of interest to women.

Articles about pilot-wives and the adventures of a physician's wife in learning about Japanese geisha girls are part of the first issue's contents. The four-color cover features a painting by abstract-expressionist Hans Hofmann.

Approximately 90,000 copies of the magazine will be distributed to members of the AMA Auxiliary, the Women's Auxiliary of the Student American Medical Association, and to officers and headquarters of other women's voluntary service organization.

MD's Wife replaces the quarterly Bulletin of the Women's Auxiliary. The editor is Mrs. John Wagner, of Clarks Summit, Pa.

Cluster of Diseases Is Identified

Sufferers from rheumatoid arthritis, peptic ulcer, or tuberculosis are also possible victims of the two other diseases.

The discovery that these three diseases form a "cluster," and sometimes strike the same victim, is reported in the September 27 *Journal of the American Medical Association.*

The same report indicates that the arthritis-peptic ulcer-tuberculosis cluster is "negatively associated" with the disease cluster of obesity, hypertension and myocardial infarction. In other words, victims of one disease cluster aren't likely to suffer from the other.

Authors of the report are Sidney Cobb, M.D., and William Hall of the Survey Research Center, University of Michigan, Ann Arbor.

For 28 months they periodically examined 244 blue-collar workers, aged 35 to 65. They used two systems of statistical comparison to gauge their medical findings.

None of the disease associations in these men were very strong, the investigators said, but the patterns were so consistent that the disease relationships are believed to be meaningful.

The association between tuberculosis and rheumatoid arthritis seems of particular significance, they said. Five men were found to have tuberculosis, and all five had some evidence of rheumatoid arthritis. In addition, three of the five had probable or definite peptic ulcers. It is highly unlikely that this could have been a coincidence, the authors said.

Fifteen men who had probable or definite symptoms of rheumatoid arthritis also had strong indications of peptic ulcers. An additional 43 men had a mixture of both arthritis and ulcer symptoms that varied from possible to definite.

Many of the findings about these disease relationships aren't new, the authors point out. What is new is the demonstration that these three diseases cluster together, and that there are now "two well-defined clusters of diseases that are negatively associated with each other."

This study was confined to men employed in a single plant. The authors note that patterns of disease association may vary with sex, ethnic origin, or geography, and that further studies are needed.

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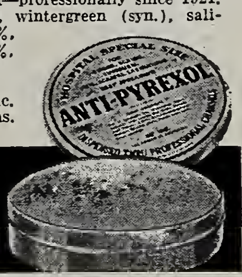

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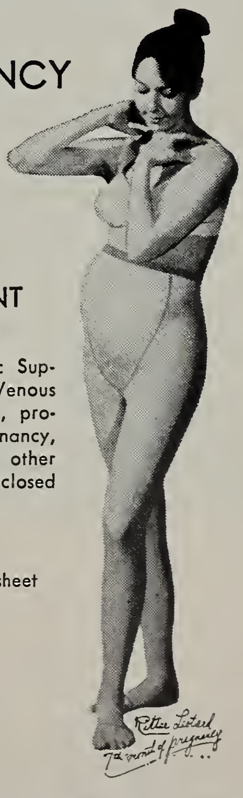

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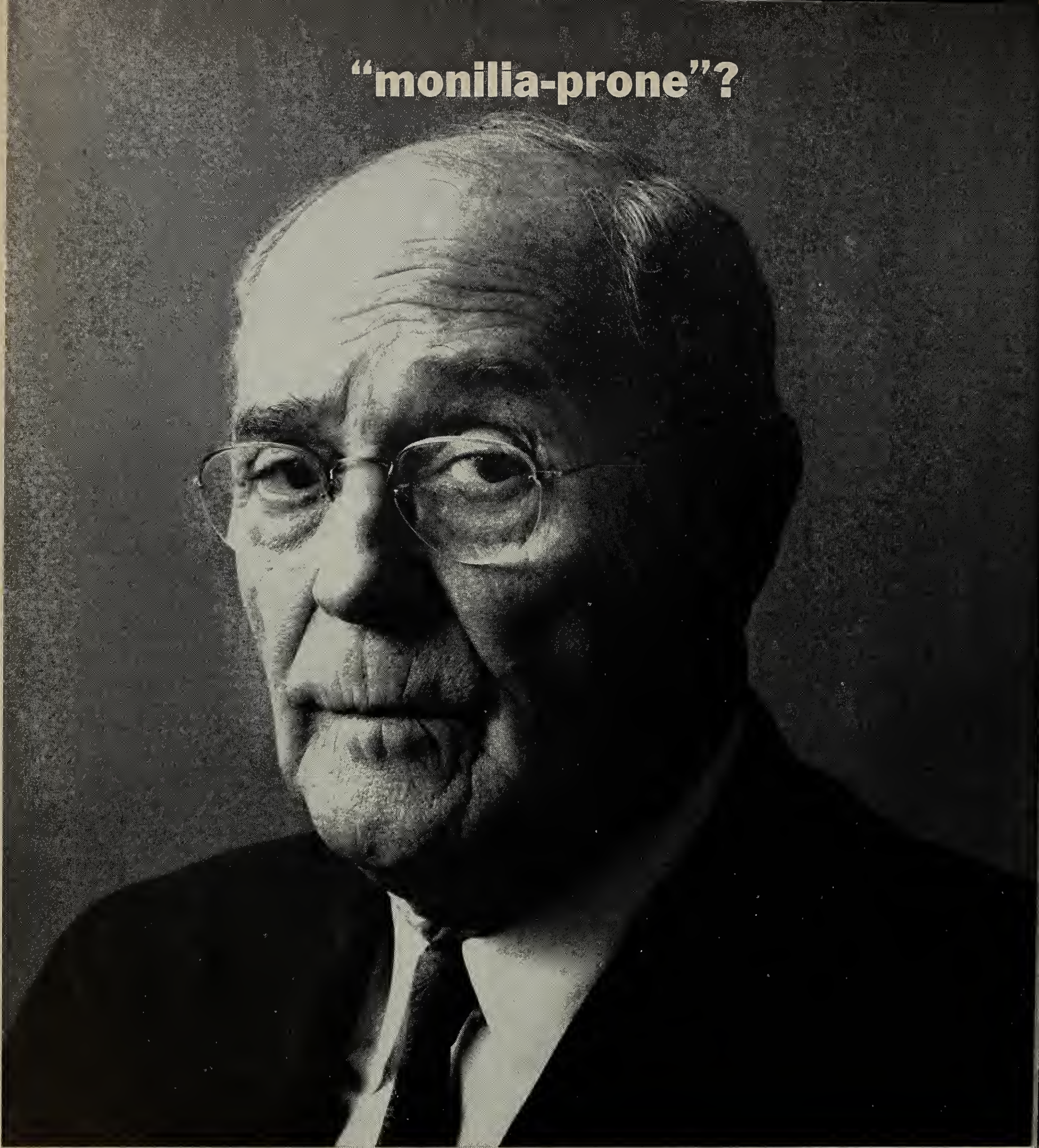
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REFERENCES AND REVIEWS

RETINOBLASTOMA: A REPORT ON 19 PATIENTS TREATED WITH RADIOTHERAPY—M. W. Paterson (12, Kirklee Rd, Glasgow, Scotland) and A. A. Charteris. Brit. J. Ophthal., 49:347-358 (No. 7) 1965.

Nineteen patients with bilateral retinoblastoma were treated with radiotherapy, using the facilities ordinarily available. Of the 13 survivors, 5 had vision of 6/12 or better, 3 had vision of less than 6/12, in one the latest vision is not recorded but is very poor, and 2 had both eyes removed. Five died of the disease and one died of intercurrent disease. Details of the radiotherapy are given in each case.

* * *

EARLY INFANTILE AUTISM AND RECEPTOR PROCESSES—E. Schopler (University of North Carolina Memorial Hosp., Chapel Hill). Arch. Gen. Psychiat., 13:327 (Oct.) 1965.

The syndrome of early infantile autism is examined as a function of the widely reported clinical observations of deviant receptor preferences. These receptor deviations are compared with normal receptor hierarchies developing from near to distance receptor dominance. Available information is consistent with the view that infantile autism involves early sensory deprivation, resulting from an interaction between a constitutional deficiency, inhibiting certain reticular arousal functions, and parental understimulation. Some implications for research and treatment are discussed.

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esulting from too rapid intravenous administration of the solution,
.V. administration should be slow, no faster than 25 mg. per min-
te, and should not exceed 100 mg. in any single dose. Particular
are should be used to insure injection only into intact veins; a
ew instances of digital gangrene occurring distal to the injection
te have been attributed to inadvertent intra-arterial injection or
eriarterial extravasation, both of which should be avoided.

NASA Issues Plasma Jet Technology Survey

A technical survey just released by the National Aeronautics and Space Administration traces the significant strides made recently in plasma jet technology.

Compiled and edited by D. W. Gates and J. B. Bond of the Marshall Space Flight Center, Huntsville, Ala.; and P. R. Dennis and C. R. Smith of Clyde Williams and Co., Columbus, Ohio, the survey says:

"Research in plasma technology and devices has tremendous potential for producing new and varied industrial processes which will add to our economic growth and development, and the results of these efforts are already being felt in the national economy.

"It has been estimated that, in addition to the benefits in defense and space, approximately $100 million has been added to the gross national product by a government expenditure of $30 million.

"In the last 10 years plasma technology has made great strides due mainly to the support of the Army, Navy, Air Force, and NASA. But some of the greatest gains are yet to come through the use of plasma-arc devices. If the level of effort increases at the present rate, the next 10 years will produce new theories, methods, equipment and

(Continued on Page 24)

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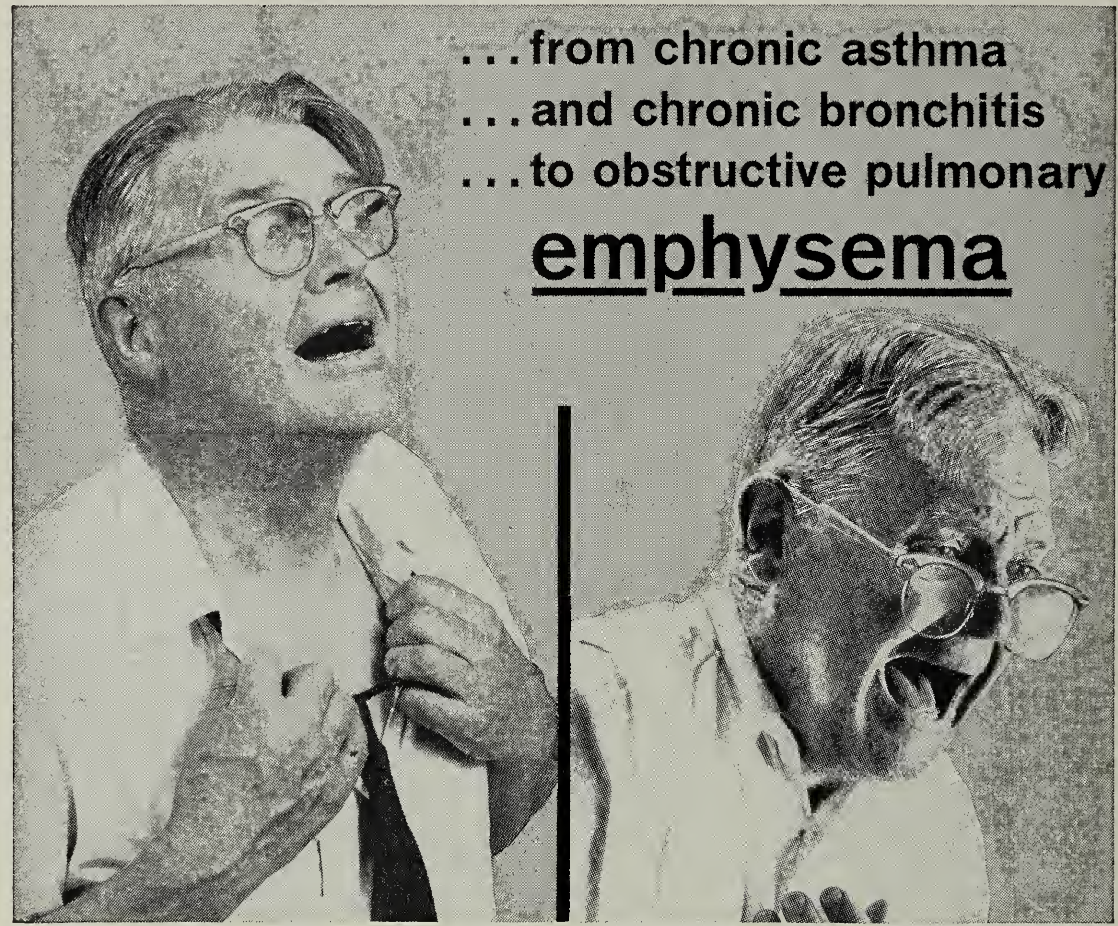

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1. Boren, H. G.: M. Clin. North America 43:48 (Jan.) 1959.
2. Jackson, R. H., et al.: Dis. Chest 45:75-85 (Jan.) 1964.

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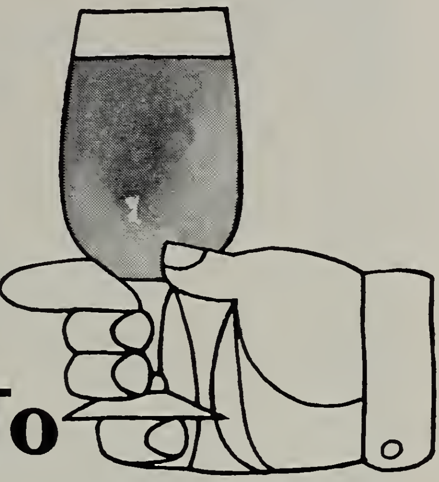

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(a few words about wine from The Winemakers of California)

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Open that wine bottle and prescribe a few ounces for your *own* stress problem . . . before, during, or after this evening's meal. As a physician, you know what stress can do to family happiness, and what wine can do for stress.* We'll be happy to send you the research findings,* at the drop of a letterhead from your office. We offer you a quarter century of our painstaking research in the relation of wine to human health.

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* Such findings as: *Greenberg, L. A., and Carpenter, J. A.: The Effect of Alcoholic Beverages on Skin Conductance and Emotional Tension; Quarterly J. Studies on Alcohol, 18:190-204 (June) 1957.*

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NASA Issues Plasma Jet Technology Survey

(Continued from Page 21)

processes which will revolutionize this field. Industrial application of many of these research developments will undoubtedly be feasible within a few years.

The survey, "Plasma Jet Technology" (NASA SP-5032), describes the current state of the art and reviews experimental work done by the space agency's Ames Research Center, Mountain View, Calif.; Langley Research Center, Hampton, a.; Lewis Research Center, Cleveland; Marshall Space Flight Center and, under contract, the Plasmadyne Corp., Santa Ana, Calif.

The new publication also lists and gives details regarding NASA plasma-arc facilities and contains a bibliography with selected abstracts to guide readers seeking more information.

Copies of the 200-page NASA Technology Utilization Division publication may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402 for $1 each.

Plea for Silver Conservation

X-ray film may become more expensive in future years, and may even be rationed in some instances.

This is because world supplies of silver are being used faster than new silver is being produced, says an article in the November 1 *Journal of the American Medical Association.* Silver halide is required in x-ray film and other photographic processes.

Conservation of silver and more efficient methods of recovering it from film processing are suggested by the article's author, Robert A. Wilson, M.D., of the Martin X-Ray and Radium Clinic and the Department of Radiology, Southwestern Medical School of the University of Texas, Dallas.

In 1964, free-world consumption of silver was 550 million troy ounces. New production was about 215 million troy ounces. Most of the difference came from U.S. silver stocks.

Even if the U.S. had produced no silver coins in 1964, free-world consumption would have exceeded silver production by 133 million troy ounces, Dr. Wilson said.

There are substitutes for conventional x-ray procedures, but they all demand greater radiation exposure of the patient or give poor image resolution or both, he said.

"The United States has been a land of plenty for so many years that it may be difficult to reestablish an ethic of conservation," Dr. Wilson said. "However, if a satisfactory substitute for silver is not found, then conservation may become increasingly important in future years."

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Precautions: *Meprobamate*—Careful supervision of dose and amounts prescribed is advised. Consider possibility of dependence, particularly in patients with history of drug or alcohol addiction; withdraw gradually after use for weeks or months at excessive dosage. Abrupt withdrawal may precipitate recurrence of preexisting symptoms, or withdrawal reactions including, rarely, epileptiform seizures. Should meprobamate cause drowsiness or visual disturbances, the dose should be reduced and operation of motor vehicles or machinery or other activity requiring alertness should be avoided if these symptoms are present. Effects of excessive alcohol may possibly be increased by meprobamate. Grand mal seizures may be precipitated in persons suffering from both grand and petit mal. Prescribe cautiously and in small quantities to patients with suicidal tendencies.

Side effects: Side effects associated with recommended doses of 'Deprol' have been infrequent and usually easily controlled. These have included drowsiness and occasional dizziness, headache, infrequent skin rash, dryness of mouth, gastrointestinal symptoms, paresthesias, rare instances of syncope, and one case each of severe nervousness, loss of power of concentration, and withdrawal reaction (status epilepticus) after sudden discontinuation of excessive dosage.

Benactyzine hydrochloride—Benactyzine hydrochloride, particularly in high dosage, may produce dizziness, thought-blocking, a sense of depersonalization, aggravation of anxiety or disturbance of sleep patterns, and a subjective feeling of muscle relaxation, as well as anticholinergic effects such as blurred vision, dryness of mouth, or failure of visual accommodation. Other reported side effects have included gastric distress, allergic response, ataxia, and euphoria.

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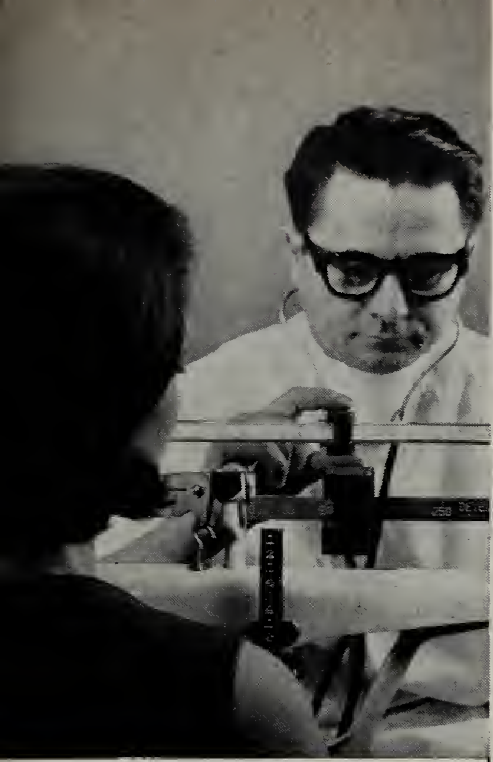

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Within Five Years
14 New Medical Schools

Fourteen new medical schools are expected to be in operation in the United States by 1970.

These will bring to 101 the nation's total of schools of medicine, and mark an "era of major expansion" in American medical education, said the November 15 *Journal of the American Medical Association.*

"Of obvious and immediate importance is the fact that 800 to 1,000 new positions will be available to qualified medical applicants," the *Journal* said. "This will help to meet the urgent national need for more physicians."

In addition to these 14 firm commitments to build schools, at least 10 other institutions "seem to be reasonably good possibilities to follow through with the development of a new (medical) school," the *Journal* said.

The new medical schools are but one of the indicators that American medical education is expanding.

The 65th annual report on medical education by the AMA's Council on Education is published in the current issue of the *Journal.* The report contains data which mark continuing gains in graduate medical education, continuing medical education, educational programs in areas allied to medicine, and programs of government agencies pertinent to medical education.

All of the new medical schools will introduce modifications of the standard medical curriculum. This should lead to "some very interesting experiments in medical education," the *Journal* said.

The new schools also will be competing for faculty with existing schools.

"This will certainly aggravate an existing manpower problem, but it will also open up new opportunities for leadership to young, vigorous medical scientists," the *Journal* said.

Over the past 20 years, the number of medical schools has increased steadily from 77 schools in 1945 to 88 in 1865. The next five years, however, will mark the period of greatest expansion.

Eight of the 14 schools being planned will provide full four-year programs leading to the M.D. degree. The other six are envisioned as two-year schools of the basic medical sciences.

"However, three or four of the latter may well progress directly to four-year programs after they have become firmly established," the *Journal* said.

The four-year schools: The University of Arizona College of Medicine, Tucson; University of California, San Diego, School of Medicine; University of Connecticut School of Medicine, Farmington; Milton S. Hershey Center, Pennsylvania State University, Hershey; Mt. Sinai School of Medicine, New York City; South Texas Medical School, University of Texas, San Antonio; University of Massachusetts, and Toledo State College of Medicine, Toledo, Ohio.

The two-year schools: Brown University Program in Medical Science, Providence, R.I.; University of Hawaii Medical School, Honolulu; Michigan State University College of Human Medicine, East Lansing; Rutgers University Medical School, New Brunswick, N.J.; University of California at Davis, and the University of New Mexico School of Medicine, Albuquerque.

The University of New Mexico accepted its first class in September 1964. As a developing two-year school, it becomes eligible for full accreditation

(Continued on Page 56)

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Illinois Community in Cancer Test

A community experiment in detection of lung cancer is completing its initial phase in suburban Chicago.

Some 6,000 residents of Park Ridge, Ill.—4,000 of them "pack-a-day" smokers or better—are expected to participate by providing samples of sputum.

The community-wide testing effort of the American Cancer Society collected more than 1,300 sets of samples during its first three weeks, Jonas Valaitis, M.D., told the Medical News section of the *Journal of the American Medical Association.*

Other investigators have shown that lung cancer may be detected as much as ten years before it becomes invasive, the pathologist explained. The sputum test being used is based on the accepted Papanicolaou technique for this purpose.

More than 100 women of Lutheran General Hospital's Service League are distributing sample vials to homes in Park Ridge and collecting them.

The women return the vials to the hospital, where Dr. Valaitis is chief pathologist. Laboratory tests are made to detect abnormal cells.

Only persons who have smoked at least one pack of cigarettes per day for about ten years or more are admitted to the smokers category of the test. In most households, both husband and wife qualify, he noted.

Families in which both husband and wife are nonsmokers are not asked to participate. Where one or the other does smoke, both are tested, with the nonsmoker serving as a control.

Other variables being taken into account include family and personal medical history, type of cigarette smoked and distance and method of travel to place of employment.

Each subject is asked to cough immediately upon rising in the morning and deposit the sputum in a sterile vial. The process is repeated for three consecutive mornings, each time with a different vial.

"In general, Park Ridge consists of young, fairly well educated people who seem highly motivated toward early cancer detection," Dr. Valaitis said. "Few refuse to participate and the great majority apparently follow test directions."

Samples are being gathered in three groups of 2,000 each during the next year.

Dr. Valaitis estimated that a minimum of 40 participants (about 1 per cent) will show cancer signs. The majority of these are expected to be among smokers, he added. Positive cases will be referred to private physicians for treatment.

Even though the sputum test has been known for more than 20 years, it has not been used on a community-wide basis comparable to mobile x-ray units. The results of the Park Ridge test, to be completed by January 1967, are expected to show whether wider application would be practical.

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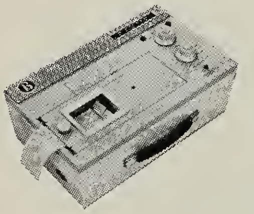

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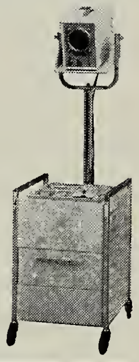

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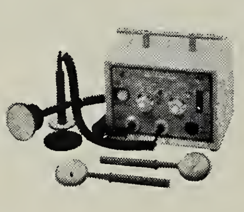

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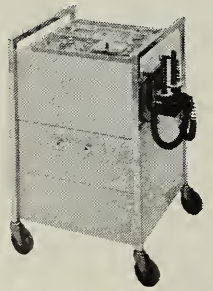

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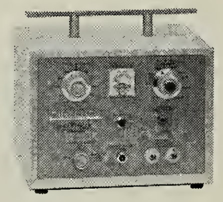

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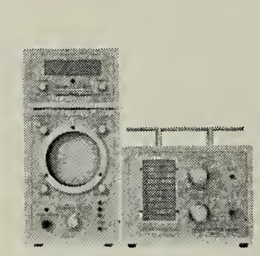

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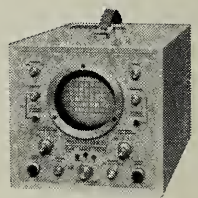

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RESPIRATORY VIRUSES

Current Status and Future Prospects

DAVID RIFKIND, M.D., PH.D., *Denver, Colorado*

■ *The application of tissue culture technology has revealed several new groups of viruses, comprising scores of different serotypes, as important causes of upper and lower respiratory tract disease in man. Other agents as yet unrecognized undoubtedly exist.*

Present epidemiologic data, although still incomplete, point up the unique importance of certain of these viruses in respiratory diseases.

The particular type and severity of respiratory syndrome produced by a virus is determined by the immune status of the host, by the presence of complicating disease and by characteristics intrinsic in the infecting agent itself.

Respiratory virus control might be particularly beneficial in certain groups, particularly persons with allergic sensitivity and chronic pulmonary disease.

For control of viral respiratory disease, active immunization would provide significant protection but highly polyvalent vaccines might be necessary. Adjuvants could be helpful in this regard.

Certain vaccines formerly in use were produced from strains of viruses which have recently been shown to be oncogenic in animals. In addition, hybridization of viruses can occur, resulting in the incorporation of the oncogenic potential of one agent into the genetic constitution of another. The significance of these biologic phenomena to vaccination programs has yet to be defined.

Passive immunization would provide short-lived protection and would find application only in uniquely susceptible populations or at times of augmented risk. Active immunization of pregnant women, however, could provide increased breadth and duration to the transplacental passive immunity in the newborn.

Interferon-inducing agents could potentially provide broad spectrum antiviral protection, but the extent and duration of their effectiveness are unknowns.

Certain chemical agents have been shown to have prophylactic and therapeutic effects against a limited number of clinically severe viral diseases. Finally, limited data suggest that climatic control in places of public gathering might be worth evaluating as a means of controlling the spread of viral respiratory infections.

Acute viral respiratory diseases make up about one-half of all illnesses of the general population.[32] It is estimated that each person in the United States has six respiratory illnesses annually,[16] that at least one of these infections is severe enough to result in a restriction of activity for an average of 3.5 days and thus account for 30 to 50 per cent of all time lost from work and 60 to 80 per cent of days lost from school.[32]

It is the purpose of this discussion to survey two particular aspects of the viral respiratory disease problem—first, the specific etiologic agents involved and, second, methods of control of these infections. In the first section, some common respiratory viruses will be described and their relative importance in the various clinical syndromes reviewed. In the second section, the present procedures for the management of these infections will be summarized and a few additional methods suggested.

Viruses of Respiratory Disease

While the virus of influenza was isolated over 30 years ago in ferrets,[37] the breadth of the respiratory virus spectrum has been revealed only in the past decade by the application of the tissue culture method to this problem. With the discovery of many new viruses, attention is now being directed toward assessing the role of individual agents as causes of the several respiratory syndromes in different age and population groups.

Virus types

Agents which are currently believed to produce significant numbers of respiratory infections are listed in Table 1. The myxovirus group is so called because of its affinity for mucopolysaccharides, a feature which determines its ability to produce clumping or hemagglutination of red blood cells *in vitro*. Included are the familiar influenza viruses and the more recently recognized parainfluenza group.[4] This latter group of viruses was first recognized by its ability to cause hemadsorption—the adherence of added red blood cells to the infected tissue culture monolayer. The four types of parainfluenza viruses affecting humans were originally designated HA-2 (hemadsorption type 2), CA (croup associated), HA-1, and M-25.

The respiratory syncytial virus (RS) is classified with the myxoviruses because of morphologic and chemical similarities although it does not show *in vitro* affinity for red blood cells. This virus was originally isolated from an outbreak of coryza in chimpanzees (CCA, chimpanzee coryza agent), the animals probably having contracted the infection from their keepers.[28]

The adenoviruses were isolated during attempts to culture adenoidal and tonsillar tissue surgically removed from children.[33] After a period of successful growth, degenerative changes occurred in the tissue explants, an effect which was shown to be due to the presence of virus carried by the children in their lymphoid tissue. These viruses were originally termed AD, or adenoid degenerating agents, and to date some 30 human serotypes have been recognized.

The picornaviruses are composed of two main groups, the enteroviruses (poliovirus, Coxsackie types A and B, and ECHO) and the rhinoviruses. while the former group can cause a variety of respiratory syndromes, its relative importance in this regard is not great. The rhinovirus groups are agents that can be recognized in cases of mild upper respiratory tract disease by altering the standard techniques and conditions used for viral isolation.[41] These modifications included the use of a lower temperature of incubation (33°C instead of 36°C), by increasing the acidity of the tissue culture medium and by incubating the tissue culture tubes on a roller drum so that the tissues are alternately bathed and then freed of medium. The agents included in this group are the Salisbury agents isolated at the Common Cold Research Unit in England, and the rhinoviruses and coryzaviruses isolated in this country. The number of serotypes is as yet unknown but is estimated to exceed 50.

The reoviruses were originally designated ECHO Type 10,[34] but they have been separated from the enteroviruses because they are larger and cause a different type of cytopathic effect in tissue culture. This group occurs in a wide variety of animals as well as in man. The name *respiratory enteric orphan viruses* (reoviruses) recognizes occurrence of these agents in both the gastrointestinal and respiratory tracts.

Psittacosis is included although this type of viral pneumonia is rare and limited to certain occupational groups. The cold agglutinin-positive primary atypical pneumonia, *Mycoplasma pneumoniae* or

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Presented at the Contra Costa County Medical Symposium on Tuberculosis and Other Respiratory Diseases, El Cerrito, California, 27 February 1965. The author is Assistant Professor of Medicine, University of Colorado Medical Center, Denver.

Submitted 16 March 1965.

Eaton agent is usually considered etiologically with the "viral pneumonias" although it has recently been shown to be a member of pleuropneumonia group of filterable bacteria.[26] Excluded from this consideration are infectious mononucleosis, for which no etiologic agent has been identified and, somewhat arbitrarily, the childhood exanthems.

Respiratory syndromes

The types of disease produced by respiratory viruses range from pneumonia through undifferentiated febrile respiratory disease to mild afebrile upper respiratory infection (reviewed by Dowling Lefkowitz[6] and Parrott and coworkers[30]). The myxoviruses, influenza, parainfluenza, and RS virus cause, with varying degrees of frequency, pneumonias, bronchiolitis, croup, febrile respiratory disease and mild afebrile colds. The adenoviruses produce a similar spectrum of illness but in addition can produce exudative pharyngitis, keratitis and conjunctivitis. Rhinovirus infection results almost exclusively in mild upper respiratory symptoms. The reoviruses, although originally isolated from the stool of children with steatorrhea, are the cause of only a small proportion of cases of undifferentiated respiratory disease.

The factors that determine what respiratory syndrome results from a viral infection include the immune status of the host, the presence of complicating disease and the nature of the virus itself. The importance of these factors is illustrated in the case of RS virus infection. The serious forms of this disease, including pneumonia, bronchiolitis and croup, occur in infants and children who are experiencing their first contact with the virus and are therefore devoid of specific antibody. Upon recontact with the virus, the host, having earlier acquired some degree of immunity, may have mild upper respiratory tract disease. Reinfection never results in severe illness.[22]

A second factor which influences the disease accompanying RS virus infection is the preexistence of other complicating disease, such as an allergic diathesis. Lower respiratory tract involvement, as evidenced by wheezing, was present with RS virus infection in 50 per cent of children with a history of allergic disease, as compared to only 17 per cent of children without such history.[10]

Finally, the difference between the overall 52 per cent incidence of wheezing with RS virus infection in this group, as compared with 21 per cent with the parainfluenza viruses and only 13 per cent with the adenoviruses,[10] suggests that features intrinsic in the viruses themselves also influence what disease is produced.

Relative incidence

While a number of viruses have now been implicated in respiratory infections, the contribution of each to the sum of all disease has not been fully defined. There are at least three causes of difficulty in obtaining such information. First, respiratory virus surveys require specially trained personnel supplied with materials and equipment for the isolation of agents, as well as batteries of costly and often rare reference antisera for their identification. Second, reported data often pertain to a single outbreak of an infection in which the overall importance of the particular agent in question is magnified. Third, data on infections in particular closed populations, such as children's homes or military installations, may not be pertinent to other

TABLE 1.—*Agents of Respiratory Disease in Man*

			*Per Cent of Respiratory Illness**			
			Infants and Children		*Adults*	
Group	*Species*	*Number of Serotypes*	*OPD*	*Hospital*	*OPD*	*Hospital*
Viruses						
Myxovirus	Influenza	3	2	16	9	13
	Parainfluenza	4	7	10	3	4
	Respiratory Syncytial	2	17	27	4	2
Adenovirus		30	5	7	4	2
Picornavirus	Rhinovirus	50+	4	0	35	0
Reovirus		3	1	0	0	0
Bedsonia	Psittacosis	1	0	0	0	2
Bacteria						
Mycoplasma	Eaton Agent PPLO	1	0	10	0	24
Bacteria			0	0	5	8
Total Per Cent Identified			36	70	60	55

*Adapted from Hilleman and coworkers.[14]

groups. Data from the combined laboratory study and literature survey by Hilleman and coworkers[4] (Table 1), however, serve for an approximation of the relative importance of the several respiratory agents in the general population. It is assumed that in general the patients treated in the outpatient department had disease of a milder nature, while those who were treated in hospital had the more severe forms of infection, frequently with involvement of the lower respiratory tract.

In children severe respiratory disease is caused largely by the myxoviruses and to a lesser extent by adenoviruses and the Eaton agent. Mild respiratory disease results from myxoviruses as well as adenoviruses. The particular importance of RS virus in children is apparent.

In adults, disease of the lower respiratory tract results primarily from influenza viruses and the Eaton agent. The majority of cases of mild infection of the upper respiratory tract in which the organism can be identified are caused by the rhinoviruses.

It should be noted that a causative agent could be found in one-third to two-thirds of the cases of respiratory infection studied. The relatively large proportion of cases for which no causative agent could be identified gives an indication of the unknowns which remain in this field.

Methods for Respiratory Virus Control

Indications for protection

Studies on the incidence of the several virus groups in severe and mild respiratory disease suggest the priority for the composition of vaccines to be used in the general population. It seems possible, however, that in certain specific groups, more intensive protection directed against even a wider variety of viruses would be beneficial. The high incidence of adenovirus infection, particularly types 4 and 7, in military recruits is an example.[12] Limited studies on patients with chronic bronchitis and emphysema suggest the possibility that acute episodes of respiratory disease could be caused, or at least triggered, by viral infections.[3] In addition, the finding that allergic sensitivity increases the severity of certain viral respiratory infections[10] indicates that this group might benefit from a broad antirespiratory virus prophylactic program. Also, the studies showing the augmenting effect of influenza virus on urethane-induced lung tumors in mice[19] could suggest that decreasing the frequency of viral respiratory might in time influence the incidence of pulmonary neoplasms.

Active immunization

The utility of active immunization, whether produced by live or killed vaccines, must be evaluated in the light of the role of antibody in protection against viral infection. As was previously noted, immunity will provide protection against lower respiratory tract infection but unless this resistance is of a high order, reinfection, with mild upper respiratory tract symptoms, may occur. In practical terms this means that a vaccine which may be satisfactory to prevent lower respiratory disease may not be potent enough to protect against upper respiratory tract illness.

Currently, most vaccine methods utilize tissue culture for the propagation of virus, whether this be for killed or live antigens. While this has provided a highly practicable source of vaccine, the procedure must be carefully controlled so that extraneous virus derived from the tissue culture is excluded from the final product. The most commonly used cell source, rhesus monkey kidney, has been shown, on occasion, to be contaminated with B virus, a herpes virus of monkeys which produces fatal encephalomyelitis in man.[18]

Of much greater frequency is the finding in such tissue culture of a number of other viruses which produce latent and subclinical infections in monkeys.[39] One such simian virus, SV40, has been shown recently to possess unique biologic properties which could have pertinence to current vaccine programs. This agent is found in high titer in rhesus monkey kidney tissue culture. It was not previously recognized, as it produced no cytopathic effect. However, when transferred to African green monkey kidney tissue culture, it produced vacuolization of the cells, hence the original name, *vacuolating agent*.[38] The virus was recently found to produce undifferentiated sarcomas when inoculated into newborn hamsters[7] and rats.[31] No SV40 virus or viral antigen could be found in the transformed sarcoma cells. However, a completely new and specific antigen, designated "T" (tumor), has been identified which does not occur in either normal hamster cells or in the SV40 virus particle itself.[35] Live SV40 virus has been demonstrated in some of the early killed adenovirus vaccine, and in both the Salk and Sabin type polio vaccines[11] which were manufactured prior to the new safety regulations. The virus is not infectious when administered orally. However, when it is given parenterally, antibody titers suggestive of viral replication are found. When SV40 was given by the intranasal route during a study of respiratory syncytial virus, evidence for infection in the form of virus isolations or antibody production was demonstrated in 23 of the 35 volunteers tested.[29] While relatively extensive follow-up studies have revealed no untoward consequences of SV40 virus infection,[9] current regulations require that virus seed and tissue cultures to be used for vaccine production be certified free of SV40.

More recently, certain adenovirus types, notably 12 and 18, have been shown to be oncogenic in newborn hamsters in a fashion analogous to that of SV40.[40] In these, as in SV40 sarcomas, no virus or viral antigen can be detected in the tumors but an adenovirus-specific tumor antigen is formed. Antibodies to the "T" antigen appear in the serum of the affected hamsters.

Within the last year or so a phenomenon of considerable biologic interest and potential medical importance has been recognized in the induction of tumors in hamsters by a particular strain (L.L.) of adenovirus type 7.[17] Serum from hamsters with such tumors was found to contain antibodies not only to adenovirus "T" antigen but also to SV40 "T" antigen. This L.L. strain of adenovirus had originally been isolated in rhesus monkey kidney tissue culture which contained SV40 but was cleared of this simian virus by several passages in African green monkey kidney tissue cultures containing SV40 antiserum. As no SV40 virus could be detected in the adenovirus preparation given to the hamsters, it would appear that some SV40 genetic information had been incorporated into the adenovirus 7 genome, resulting in a hybrid virus. These observations indicate the possibility that the oncogenic potential of one virus (SV40) can be added to the hereditary constitution of a second agent, in this case an adenovirus employed for vaccine production. The significance of these observations to man is as yet unknown.

In order to eliminate the as yet poorly defined potential hazard of extraneous agents in vaccines, clinical trials of adenovirus immunization, using purified viral fractions or subunits rather than the whole virus particle itself, are in progress.

Virus particles are, in general, composed of a core of nucleic acid, either desoxyribonucleic acid (DNA) or ribonucleic acid (RNA), and a coat of protein molecules arranged on the core in an orderly and geometric fashion. The function of the nucleic acid is to store the viral genetic information and to direct multiplication within the infected cell. In the case of poliovirus the coat can be removed by phenol extraction, leaving the naked RNA core which under appropriate ionic and osmotic conditions can itself infect cells.[15] This new virus induced by the infectious RNA is, of course complete, coat and all, since the information for determining the structure of the particle resides in the nucleic acid. The function of the protein coat is to permit efficient attachment of the virus to the cell, and to protect the nucleic acid core from destructive enzymes present in the host. However, most important to this consideration of vaccines is that the protein coat is the antigenic component of the virus particle; and antibody produced to this component protects the host against infection by preventing viral attachment to the cell. The protein coat, therefore, is the essential virus subunit in a vaccine. By appropriate chemical methods the protein coat can be removed from the virus particle, purified and used as a vaccine. Such products would be free of any potentially oncogenic nucleic acid and would be less likely to contain extraneous agents.

While these experimental purified vaccines are currently being prepared by the chemical fractionization of complete viral particles, it might be possible to by-pass this step by producing viral subunits directly rather than whole viruses. For example, in the presence of the inhibitor 5-fluorouracil, pseudorabies virus infection in rabbit kidney tissue culture will result in the formation of coat protein but no complete virus. The growth of virus in the presence of appropriate inhibitors could not only eliminate the need for fractionation, but also for inactivation of the vaccine—procedures which in general tend to cause some loss of antigenic potency.

Adjuvants may be incorporated in a vaccine when the quantity of antigen which can be administered is limited, either by complexities of manufacture as with purified subunits, or by the number of different antigens to be incorporated in a polyvalent product. Such materials have been shown to decrease the quantity of antigen and the number of injections required to produce an antibody response. The use of such adjuvants has been attended by no serious consequences and only rare local reactions.[27] Recently a new product, adjuvant 65, has been developed which substitutes metabolizable peanut oil for the non-metabolizable mineral oil of Freund's incomplete adjuvant.[13] The use of such adjuvants may prove of fundamental importance in the preparation of vaccines containing large numbers of antigens, particularly if the relatively costly purified viral protein subunits are used.

Passive immunization

Passive immunity produced by pooled human gamma globulin has been utilized in several viral diseases, particularly hepatitis, measles, mumps, varicella and vaccinia.[8] Because the half-life of globulin is approximately thirty days, the immunity resulting from a single injection is relatively short lived. This mode of protection would be of value only at times of high risk or in patients uniquely susceptible. Examples of these would be during a nursery epidemic or in patients receiving suppressive drug therapy for malignant or autoimmune disease.

Natural passive protection is supplied to the newborn by the transplacental transmission of antibody. This protection is, of course, qualitatively specific, reflecting the immune status of the mother, and is quantitatively related to the maternal antibody titer. It should be possible, therefore, both to extend the spectrum of newborn passive viral immunity and to increase its duration by a course of active immunization of the mother during gestation. Inactive vaccines would undoubtedly be preferable for this use because of the undefined teratogenic hazard which might obtain with live virus preparations.

Interferon

A substance was found in the supernate of chick embryo cells infected with influenza virus which protected fresh cells from such an infection.[20] This substance, termed *interferon,* is produced in a wide variety of tissue cultures during virus infection and has been demonstrated in the serum of animals and man. Interferon is a protein of low molecular weight which does not inactivate preformed virus but rather prevents the cell from synthesizing new particles.[25] The specificity of interferon is host cell oriented rather than virus oriented; that is, interferon produced in chick embryos will protect chicken cells against a wide variety of viruses, but such interferon will have little protective effect for cells of mouse or monkey origin. A clinical trial has demonstrated that the intradermal inoculation of interferon into volunteers will decrease the frequency and severity of vaccination takes.[36]

It should be noted, however, that infectious virus is not required to induce cells to produce interferon; the process can be initiated by inactive virus, viral nucleic acid or actually by any nucleic acid foreign to the cell.[21] Prophylaxis against respiratory viruses then might be induced by spraying the nasopharynx with an appropriate interferon-inducing preparation. The resulting protection would theoretically have the advantage of being broad spectrum rather than species-specific as a vaccine would be, a feature which would be of particular value when the numbers of viruses involved in upper respiratory disease are considered.

Antiviral agents

There are currently three principal types of antiviral agents which are undergoing clinical trials (Table 2). The first, iododeoxyuridine (IUDR), is effective against members of the herpesvirus group and has been found to be useful in the topical treatment of herpetic keratitis.[23] This compound is a nucleic acid inhibitor which blocks

TABLE 2.—*Spectrum of Antiviral Agents*

Agent	*Virus Inhibition* *Desoxyribonucleic Acid (DNA)*	 *Ribonucleic Acid (RNA)*
Iododeoxyuridine	Herpes simplex Varicella-zoster? Vaccinia	
Cytosine arabinoside	Herpes simplex Varicella-zoster? Vaccinia	
Methyl isatin B-thiosemicarbazone	Smallpox Vaccinia Varicella-zoster?	
Adamantanamine		Influenza Parainfluenza Respiratory Syncytial Rubella

the incorporation of thymidine into DNA. Another agent of this general type is cytosine arabinoside, also used in herpetic keratitis, which acts by competing with cytosine deoxyriboside for incorporation into nucleic acid.[24]

The second type is methyl isatin B-thiosemicarbazone, or methisazone, which has recently been shown to protect against smallpox.[1] In a field trial in Madras, this agent when administered to persons who were in household contact with patients who had smallpox, reduced the incidence of secondary cases almost 20-fold. Of particular interest was the finding that the contacts who received methisazone showed an immune reaction upon subsequent vaccination. Apparently, despite the administration of methisazone, sufficient viral protein was produced to stimulate the hosts' antibody producing mechanisms. Thus, the drug protected against clinical disease but still permitted the development of active immunity.

The newest antiviral agent to be tested is 1-adamantanamine, or amantadine.[5] This compound, in contrast to the two previously described, is effective against RNA rather than DNA viruses, and is believed to act by slowing penetration of virus into the host cells. Little clinical data are available thus far, but the drug is being evaluated as a possible anti-influenza prophylactic agent.

Climatic control

The economic consequences of mild respiratory disease, caused to a significant extent by the rhinoviruses, has been stressed and the desirability of control is apparent. However, because of the large number of antigenic types involved, a vaccine would be technically difficult to prepare; and because of the possibility of reinfection, high vaccine potency would probably be required. On the other hand, if an antiviral agent were available it would have to be singularly free of toxic side-effects for its use to be justified in so benign and self-limiting a disease.

A possible alternative method of controlling this type of widespread but mild type of illness is suggested by the effects of climatic conditions on certain viral respiratory diseases. For example, an outbreak of Coxsackie A-21 respiratory disease in a military population ended when there was an abrupt drop in the relative humidity and temperature.[2] It might be possible to decrease the viability and transmission of respiratory viruses by controlling various climatic conditions, including temperature, humidity, rate of air change and concentration of suspended particles. These measures, if effective, would be applicable to places where relatively large numbers of people aggregate—schools, theaters, factories and the like.

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CEPHALOTHIN

Its In Vitro Antibacterial Spectrum as Studied in a Diagnostic Laboratory

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■ *Of 655 bacterial strains isolated in a routine clinical diagnostic laboratory, 564 (86 per cent) were found sensitive to cephalothin by disk sensitivity test. However, the fraction of sensitive Gram-negative bacilli and enterococci declined sharply at concentrations approximating those obtained in serum after the usual recommended dosages. Gram-positive bacteria remained sensitive throughout the entire range of testing concentrations.*

Unless very high dosages are used, cephalothin cannot be considered a broad-spectrum antibacterial agent for use while cultures are pending. Even with very high dosages all strains of Pseudomonas spp. *and significant fractions of other Gram-negative bacillary species remain resistant to cephalothin.*

If used alone, the high potency cephalothin disk may yield inadequate information and should be supplemented by a lower potency disk, standardized measurements of zone diameters, or a screening plate.

A NEW antimicrobial, cephalothin (Keflin®, Lilly), is bactericidal, effective against Gram-positive and Gram-negative bacterial species *in vitro* and *in vivo,* devoid of inherent toxicities and resistant to degradation by staphylococcal penicillinase.[1,3,5,9] Cephalothin is chemically related to the penicillins, but does not produce crossed allergic hypersensitivity reactions. Minor, thus far reversible, cutaneous hypersensitivity reactions, eosinophilia and transient neutropenia have been reported.

The potential usefulness of cephalothin in the treatment of infections due to Gram-positive cocci and some Gram-negative bacteria prompted a comparison of the *in vitro* sensitivity-resistance patterns of bacteria isolated in a routine diagnostic laboratory to cephalothin and other antimicrobials.

Materials and Methods

All specimens submitted for culture and antibacterial sensitivity determinations to the Infectious Disease Laboratory at the Palo Alto-Stanford Hospital Center between 21 December 1964 and 11 February 1965 were processed with plate screening tests. No attempt was made to control inoculum size.

Primarily to test Gram-positive cocci, plate concentrations of 1.0 unit per ml for penicillin-G and 2 mcg per ml for erythromycin were chosen to approximate the concentrations attained in serum after commonly employed dosages. Each ampicillin, neomycin, streptomycin, tetracycline and chloramphenicol plate contained 10 mcg per ml, and each colistin plate 5 mcg per ml, to approximate *peak* serum concentrations after full dosages.

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Each isolate was also tested against the commercially available 30 mcg cephalothin disk (Baltimore Biological Laboratories). This concentration is very high compared to the serum concentrations achieved after usual dosages of cephalothin.[6] Three cephalothin screening plates were employed to avoid difficulties in comparing results obtained by the disk method with those from the plate screening technique. One plate contained 5 mcg per ml to approximate the mean concentration anticipated after the recommended dosage of 0.5 gm intramuscularly.[4,6] The second contained 10 mcg per ml to approximate the *peak* concentrations with 0.5 gm intramuscularly.[4,6] The third plate contained 20 mcg per ml to approximate *peak* serum concentrations attained after the administration of 1 gm intramuscularly.[4,6] Similar and even higher concentrations are achievable after intravenous therapy.[6]

Susceptibility was determined by absence of growth on the screening plates or by any zone of inhibition around the 30 mcg cephalothin disk after incubation of the plates at 37°C for 16 to 18 hours.

To assess further the *in vitro* sensitivities of various microorganisms to cephalothin, all strains resistant to 20 mcg per ml by the plate screening technique, but sensitive to the 30 mcg disk under the conditions described, were evaluated by the tube dilution method. One tenth ml of a 1:100 dilution of a 24-hour broth culture of the test organism was added to a series of tubes containing 2.0 ml of brain heart infusion broth and cephalothin in concentrations of 5, 10, 20, 30, 40, and 100 mcg per ml. The minimum inhibitory concentration (MIC) was recorded as the lowest concentration of cephalothin required to inhibit growth after 24 hours of incubation at 37°C. These microorganisms were further studied by repeating the plate screening and disk studies, using standard heavy inocula. The blood agar plate surface was streaked once with a cotton swab from an undiluted overnight broth culture of the test organism.

Results

The laboratory received 3,168 specimens originating from diverse clinical sources; 655 were subjected to sensitivity testing. The microorganisms tested and their sensitivity patterns to the various antimicrobials are shown in Tables 1 and 2.

Of the 655 isolates, 563 (86 per cent) were sensitive to the 30 mcg cephalothin disk, with similarly wide ranges exhibited only by chloramphenicol (85 per cent) and neomycin (81 per cent).

TABLE 1.—*Sensitivity of 655 Bacterial Isolates to Cephalothin*

				Plate Screening Tests					
		30 mcg disk		*20 mcg/ml*		*10 mcg/ml*		*5 mcg/ml*	
Bacterial Species	*No. of Strains*	*No.*	*Per Cent* *	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*
Staph. aureus	194	194	100.0	193	99.5	193	99.5	193	99.5
Staph. albus	64	64	100	64	100	64	100	64	100
Nonhem. strepto.	37	37	100	37	100	36	97	36	97
Pneumococcus	4	4	100	4	100	4	100	4	100
Hemolytic strepto.	14	14	100	14	100	14	100	14	100
Enterococci	16	15	94	13	81	4	25	3	19
Diphtheroids	6	6	100	6	100	6	100	6	100
Bacillus spp.	1	1	100	1	100	1	100	1	100
Total Gram-positive	336		99.7		98.8		95.8		95.5
Escherichia coli	138	115	83	75	54	55	40	30	22
Klebsiella-Aero.	47	32	68	25	53	16	34	13	28
Pseudomonas	37	0	0	0	0	0	0	0	0
Proteus (Indol+)	25	21	84	20	80	20	80	14	56
Proteus (Indol−)	30	26	87	23	77	17	57	11	37
Paracolon	10	9	90	5	50	2	20	1	10
Salmonella	1	1	100	1	100	1	100	0	0
Herellea	3	1	33	0	0	0	0	0	0
Providence, Mima, Serratia, Bacteroides	8	3	38	1	13	1	13	1	13
Neisseriae	20	20	100	20	100	17	85	17	85
Total Gram-negative	319		71.5		53.3		40.4		27.3
Total bacterial isolates	655		86.0		76.8		69.0		64.0

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* If fractions not included, per cent rounded off to nearest integer.

TABLE 2.—*Sensitivity of 655 Bacterial Isolates to Various Antimicrobials*

Bacterial Species	*No. Str.*	*Pen-G*		*P-50**		*Strepto.*		*Tetra.*		*Chloro.*		*Erythro.*		*Neomycin*		*Colistin*	
		No.	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*
Staph. aureus	194	88	45	108	55	150	77	153	79	188	97	181	93	189	97	0	0
Staph. albus	64	24	37	41	64	47	73	34	53	58	91	59	92	64	100	0	0
Nonhem. strep.	37	37	100	37	100	0	0	27	73	37	100	37	100	0	0	0	0
Pneumococcus	4	4	100	4	100	0	0	4	100	4	100	4	100	0	0	0	0
Hem. strep.	14	14	100	14	100	0	0	10	71	14	100	14	100	0	0	0	0
Enterococci	16	0	0	16	100	0	0	5	31	16	100	15	94	0	0	0	0
Diphtheroids	6	6	100	6	100	5	83	6	100	6	100	5	83	6	100	0	0
Bacillus spp.	1	0	0	0	0	1	100	1	100	1	100	1	100	1	100	1	100
Total Gram-positive	336		51.5		67.3		60.4		71.4		96.4		94.0		77.4		0.3
E. coli	138	0	0	85	62	108	78	104	75	130	78	0	0	135	98	78	57
Kleb.-Aero.	47	0	0	5	11	33	70	37	78	35	75	0	0	44	94	24	51
Pseudomonas	37	0	0	0	0	0	0	2	5	0	0	0	0	3	8	30	81
Prot. (Ind.+)	25	0	0	21	84	21	84	2	8	19	76	0	0	25	100	0	0
Prot. (Ind.−)	30	0	0	24	80	25	83	0	0	17	57	0	0	28	93	3	10
Paracolon	10	0	0	6	60	8	80	9	90	9	90	0	0	9	90	5	50
Salmonella	1	0	0	1	100	1	100	1	100	1	100	1	100	1	100	0	0
Herellea	3	0	0	0	0	3	100	2	67	0	0	0	0	3	100	3	100
Providence, Mima, Serratia, Bacteroides	8	0	0	0	0	1	13	3	38	2	25	1	13	7	88	1	13
Neisseriae	20	8	40	20	100	18	90	18	90	20	100	11	55	18	90	2	10
Total Gram-negative	319		2.5		50.8		68.3		55.8		73.0		4.1		85.6		45.8
Total bacterial isolates	655		27.6		59.2		64.3		63.8		84.9		50.2		81.4		22.4

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* Ampicillin
See text for concentrations of antimicrobials.
Fractions rounded off to nearest integer.

When lower concentrations of cephalothin were investigated, only 418 (64 per cent) of all isolates were inhibited at 5 mcg per ml and 451 (69 per cent) at 10 mcg per ml. These figures are comparable to those for ampicillin (59 per cent), streptomycin (64 per cent) and tetracycline (64 per cent).

When only Gram-positive bacterial species were examined, all concentrations of cephalothin tested yielded greater than 95 per cent inhibition, results similar to those obtained with chloramphenicol (96 per cent) and erythromycin (94 per cent). Cephalothin was more efficacious than ampicillin against staphylococci, which accounted for two-thirds of the Gram-positive isolates, while ampicillin was more effective against enterococci. Penicillin-G inhibited only 52 per cent of the Gram-positive bacteria. Staphylococci and enterococci accounted for the greatest fraction of Gram-positive cocci that were resistant to penicillin-G.

The sensitivity of Gram-negative bacilli to cephalothin diminished sharply as the test concentration declined. Of the 319 Gram-negative bacterial isolates, 71 per cent were sensitive to the 30 mcg disk, 54 per cent to the 20 mcg per ml, and 41 per cent to the 10 mcg per ml, but only 27 per cent to the 5 mcg per ml concentration. Of the same strains, 51 per cent were sensitive to 10 mcg per ml of ampicillin, which was slightly more effective than cephalothin at comparable concentrations. In declining order, neomycin, chloramphenicol, streptomycin and tetracycline were also more effective than cephalothin against Gram-negative bacilli. The overall effectiveness of colistin fell between the 10 and 20 mcg per ml concentrations of cephalothin and below those of neomycin, chloramphenicol, streptomycin, tetracycline and ampicillin. However, colistin inhibited 30 (81 per cent) of 37 Pseudomonas strains against which all of the other antimicrobials were essentially ineffective.

Ampicillin was more effective than cephalothin against *E. coli* and *Proteus mirabilis.* Only the 30 mcg cephalothin disk showed greater efficacy against these two bacterial species than did ampicillin. Cephalothin was somewhat more effective than ampicillin against members of the *Klebsiella-Aerobacter* group.

Of the 61 strains found to be resistant to the 20 mcg per ml screening plate, but sensitive to the 30 mcg disk of cephalothin, 37 were studied by the tube dilution method. The results are shown in Table 3.

TABLE 3.—*Tube Dilution Studies of Strains Resistant to 20 mcg per ml Screening Plate and Sensitive to 30 mcg Disk.*

	Cephalothin Minimum Inhibitory Concentration (mcg/ml)						
Organism	*5*	*10*	*20*	*30*	*40*	*>100*	*Total*
E. coli	1	0	8	13	2	1	25
Klebsiella-Aerobacter	1	0	2	0	1	2	6
Paracolon	0	0	1	1	0	0	2
Proteus mirabilis	0	0	0	0	2	1	3
Enterococcus	0	0	0	1	0	0	1

On repeat examinations with controlled inocula, 28 of the 37 strains yielded the same results as when the inoculum size was not controlled; four were resistant to the 30 mcg disk, and for all of these the MIC was more than 100 mcg per ml; and five were sensitive to the 20 mcg per ml but resistant to the 10 mcg per ml screening plate. The MIC was 30 mcg per ml for four of these strains and 40 mcg per ml for the fifth strain.

Discussion

Cephalothin is a valuable addition to the therapeutic armamentarium. However, it is not the universally effective agent so often desired in complicated instances of hospital-acquired infection and superinfection commonly encountered in patients whose defense mechanisms may be seriously compromised by disease or therapy. Currently its main role appears to be in the treatment of penicillin-G resistant staphylococcal infections in patients allergic to the penicillins.

The data presented show that cephalothin possesses a wide range of antibacterial activity. However, this requires qualification. Of 655 diverse strains isolated from a variety of clinical sources involving most organs and tissues of the body, 563 (86 per cent) were inhibited by the 30 mcg cephalothin disk. Cephalothin inhibited all staphylococci regardless of their susceptibility to penicillin-G, as did methicillin (data not included in this report). At the highest test concentration, cephalothin also inhibited all but one of 16 strains of enterococci.

Significant fractions of *Proteus spp., Klebsiella-Aerobacter,* and some other Gram-negative bacilli were resistant to 30 mcg of cephalothin, but only *Pseudomonas spp.* remained completely resistant. The anti Gram-negative bacillary efficacy of cephalothin declined sharply with test concentrations approaching those obtained in body fluids after commonly employed dosages.[6,8]

If cephalothin were used as a broad spectrum agent pending the results of culture, intramuscular or intravenous doses several times those ordinarily recommended would be required to assure adequate coverage against many Gram-negative bacilli.[6] Even then, all infections due to *Pseudomonas spp.*, many due to *Klebsiella-Aerobacter,* and almost 20 per cent of *E. coli* infections would probably not be covered.

Results from the plate screening technique were comparable to those obtained by tube dilution. Of the 37 strains resistant to the 20 mcg per ml screening plate, 24 (65 per cent) had an MIC by tube dilution of more than 20 mcg per ml and 32 (86 per cent) had an MIC of more than 10 mcg per ml.

A close correlation also existed between the disk and tube dilution techniques. Of the 37 strains initially reported sensitive to the 30 mcg disk and resistant to the 20 mcg per ml screening plate, four were resistant to the disk on repeated examinations using the standard heavy inocula. According to the techniques employed in this laboratory, sensitivity to the 30 mcg cephalothin disk probably indicates an MIC of less than 40 mcg per ml by tube dilution.

The 30 mcg disk should probably be supplemented with either a lower potency disk, standardized measurements of zone diameters or a screening plate to offer better correlations between concentrations achieved following the usual recommended dosage schedules and *in vitro* testing. In this laboratory, the 10 mcg per ml screening plate serves the purpose, as it has with ampicillin.

To date there appears to be no dose-related toxicity attributable to cephalothin other than pain at injection sites and thrombophlebitis.[6] In this respect it is potentially superior as a broad spectrum agent to neomycin and chloramphenicol, and also to ampicillin which is ineffective against the penicillin-G resistant staphylococci. Ampicillin also shares crossed allergenicity with other penicillins.

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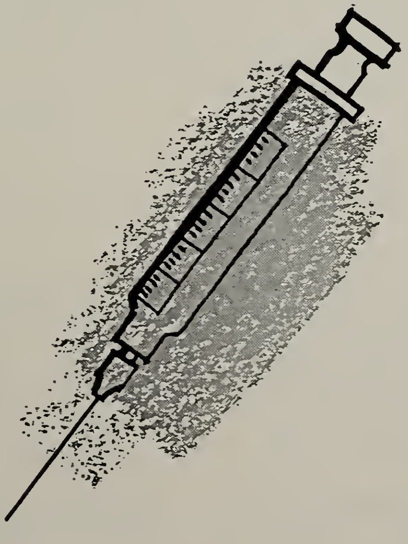

Systems for Maintenance of Urinary Sterility After Prostatectomy

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■ *Closed drainage is recommended for all patients after prostatectomy where hemostasis has been adequate. Although closed drainage can maintain sterility of the bladder, thereby fostering healing and reducing infectious complications, such drainage is not insisted upon at most hospitals because of the inconveniences associated with it. However, when closed drainage was used in 25 consecutive cases of transurethral resection, infection was reduced to 25 per cent (in contrast to the 85 to 100 per cent encountered with open drainage).*

The ideal closed system should incorporate:

1. *Fixed tubing to prevent contamination where the catheter joins the tubing and where the tubing is attached to the container;*
2. *An aseptic method of emptying;*
3. *A device to prevent reflux of the potentially contaminated urine in the container into the bladder;*
4. *Free urinary flow from bladder to container; and*
5. *Portability for the patient and convenience for the staff.*

A system is proposed that incorporates these features. Particularly effective are a fixed drip chamber with vents at the site of attachment of the tubing to the bag and a protected spigot for emptying.

THE BACTERIA THAT infect the urine after prostatectomy are most often those that have been transferred from other patients.[8,9,17,18] Less often, they come from the patient himself.[12,14] In the former instance, the ascent of bacteria from a contaminated drainage bottle appears to be the most frequent cause of infection during indwelling catheterization.[22] It is known that the vesical defense mechanism cannot rid the bladder of infection if bacteria are introduced repeatedly or in overwhelming amount.[3,4] These defenses are further reduced by presence of a foreign body (in this case, the catheter), by the instrumentation neces-

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sary for transurethral resection, and by the effects of the prostatic wound. It seems probable, therefore, that maintenance of urinary sterility after operation would reduce complications, although statistical support of this statement is not yet available.*

Catheter drainage of two to five days appears necessary for the management of patients after prostatectomy. The inconveniences and hazards of omitting it are usually greater than its harmful effects. Attention, then, must center on the most reliable and practical method of maintaining sterility of the urine for the required period of catheterization.

Since Pyrah and his group[21] reported the effectiveness of "closed drainage" after prostatectomy, numerous investigators have reported reduced incidence of post-prostatectomy infection with its use.[10] Chart 1 illustrates the typical effects. The greatest reported change was from 83 per cent infected when sterile precautions were not used to 6 per cent when such precautions were applied. If this is so, why has strict closed drainage not been universally adopted?

The answer is: It is a nuisance to maintain a sterile system. The physician and nurse wish to irrigate the catheter to keep it free from clots. The patient prefers to walk around unimpeded. The orderlies like to collect the urine without the bother of special maneuvers or techniques. Consequently, to obtain universally the benefits of keeping the urine free of infection after operation, systems must be devised that are not only effective but are acceptable to all persons concerned. In the study here reported, we examined the properties of a closed drainage system in order to suggest a more acceptable system than those available.

Requirements for "Closed Drainage"

Five factors must be present in any drainage system if it is to be used as an effective barrier to the introduction of infection:

1. Permanently affixed tubing, to prevent contamination of its junctions with the catheter and container;

2. An aseptic method of emptying the container (or, alternatively, antiseptics placed in the container);

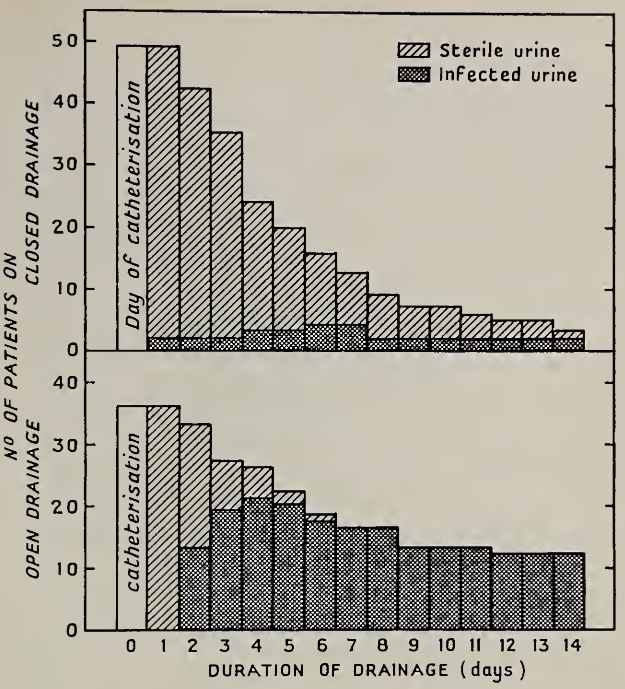

Chart 1.—Effect of open and closed drainage on the incidence of infection after prostatectomy (from Miller, A. and coworkers[14]).

3. An anti-reflux device to prevent back flow of fluid from container to bladder;

4. Free flow; and

5. Portability and convenience of use.

1. *Permanently affixed tubing.* To assure sterility, the drainage tubing must be attached aseptically to the catheter at the conclusion of the operation and taped in place to make unauthorized disconnection difficult. This should be done in the operating room, not in the recovery room. The distal end of the tubing, if permanently attached to the container, is not easily contaminated.

2. *An aseptic method of emptying the container.* A container that must be emptied by removal of a cap through which the drainage tube extends, as it does in most instances, is subject to contamination. Thus, another route for periodic emptying must be employed.

A vent that opens when the bag is tipped and closes when it is upright is the simplest mechanism but, since it is essentially open, it too carries the risk of contamination. A spigot at the bottom of the container can be closed with a valve or clamp. However, contamination of the spigot's spout can possibly result in retrograde ascension of bacteria.

3. *Devices to prevent backflow of contaminated urine from container to bladder.* Three devices

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*Since this manuscript was written Plorde and coworkers[20] have shown that surgical complications after prostatectomy were more frequent in patients with postoperative bacteruria.

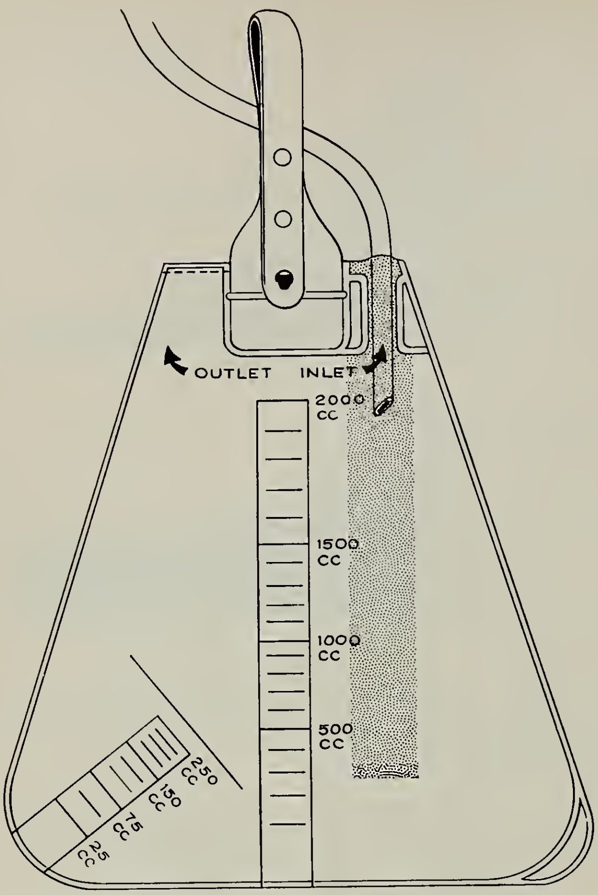

Figure 1.—Flutter valve. The Meredith drainage set, Eschmann Bros. and Walsh, Ltd., Shoreham-by-sea, Sussex, England.

are in use: (a) vents to release the urine before enough pressure is built up to produce backflow; (b) valves; and (c) chemicals in the container that render the urine sterile.

A vent, to be effective, must be at the point of inflow (for example, incorporated with the cap). Otherwise, when the container is put down (as on the edge of the wash basin while the patient is defecating), its contents may be siphoned back into the bladder.

The drip chamber has been demonstrated to be effective as a valve. A flutter valve (Figure 1) might be expected to allow ascent of bacteria along its interior interface, although experiments have not shown that this is necessarily so.[16]

Chemicals in the container may be harmful to the bladder if siphonage does occur. They are probably practical only in gallon glass jugs that are too large to be raised above bladder level and that have large vents which permit the urine to escape before it can return to the bladder. The instillation of a non-toxic antibacterial agent into the container each time it is emptied would, however, decrease the chances of vesical contamination.

4. *Free flow.* The hydraulics of catheter drainage are generally poorly understood. Drainage tubing of small diameter (3/16 inch) will usually remain filled with urine and, hence, exert a siphon effect; in large tubing (9/32 inch), the siphon is usually broken and urine levels off in the loop in balance between inflow and outflow. That back-pressure is not exerted in the smaller tubing is obvious. In the larger tubing, the fact that the meniscus in the proximal side of the loop is at the same height as that in the distal side shows manometrically that no back-pressure exists. The exceptions to this, of course, are instances in which the tubing is looped above the level of the bladder. If the tubing is looped below the level of the container, flow will continue on into the container as soon as the two sides fill to the level of the entrance to the container.

An objection to the smaller tubing is that clots may not pass through it. However, since a 24 F Foley (and red rubber) catheter has a bore of 14 F, approximately the same bore as the tubing, no obstruction should be expected unless the adapter has a smaller bore than the tubing.

For the maintenance of free flow, the container must either have vents to allow the displaced air to escape, or have easily expansible sides.

5. *Portability, and convenience to the patient and the staff.* Since ambulation is important postoperatively, the apparatus should be easily port-

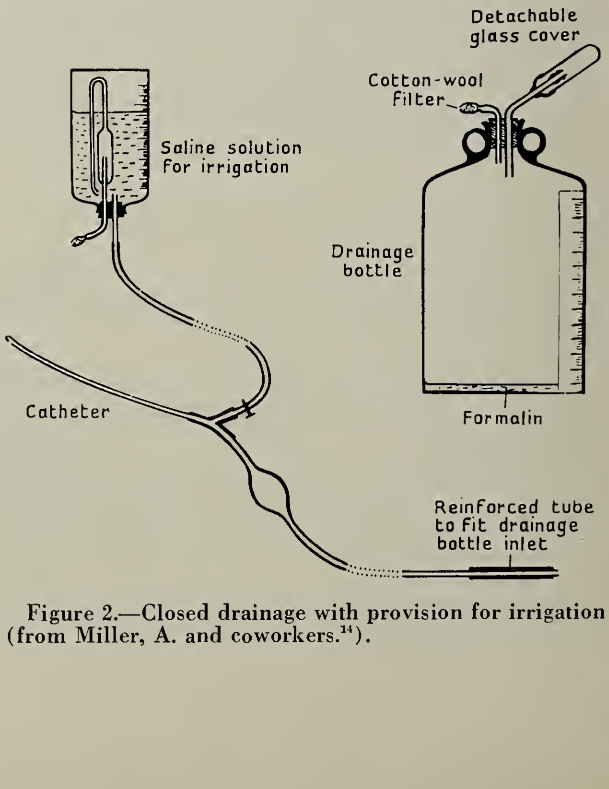
Detachable glass cover
Cotton-wool filter
Saline solution for irrigation
Drainage bottle
Catheter
Formalin
Reinforced tube to fit drainage bottle inlet

Figure 2.—Closed drainage with provision for irrigation (from Miller, A. and coworkers.[14]).

able. Construction from plastic materials has made this possible. A further convenience is a container sufficiently rigid to stand by itself. This is not essential, however, and a reasonable alternative is a flat bag that can be pinned to the patient's gown.

Convenience to the staff is a consideration not to be taken lightly. If the apparatus requires a complicated aseptic technique to maintain sterility during emptying, a break in sterility can be expected. Containers that empty by tipping or through a spigot will have a better chance of remaining sterile than those requiring disconnection of any parts.

Additional Means

Other types of closed systems not included in the preceding considerations are those arranged for intermittent or continuous irrigation. Miller and coworkers[15] described the prototype of these systems (Figure 2) incorporating a sterile reservoir, a Y-connector, an integral bulb pump and a floor container. Our limited experience with apparatus of this type, which is needed only in those cases in which significant postoperative bleeding with clots is anticipated, has not been good. Overfilling of the bladder, with consequent leakage at the site of prostatic capsular closure, has occurred. In these patients, open irrigation with aseptic precautions is more effective and, although less secure bacteriologically, assures a more satisfactory postoperative course since control of bleeding and leakage take precedence over maintenance of asepsis.

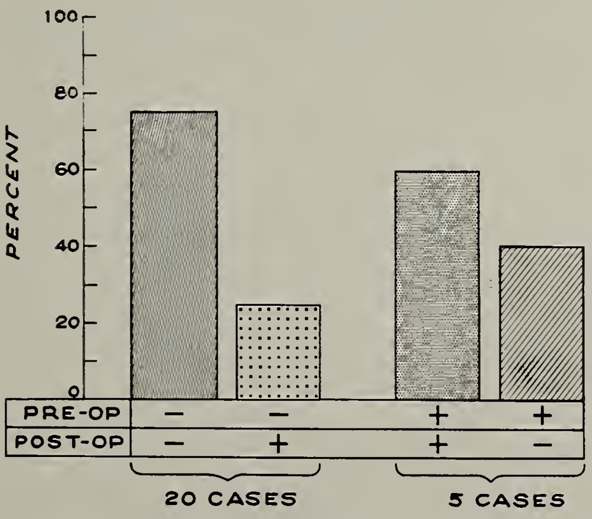

Chart 2.—Incidence of infected urine before and after transurethral resection with closed drainage in a personal series of 25 consecutive cases—20 in which the urine was sterile (−) before operation and 5 in which it was infected (+).

No discussion will be undertaken here of antiseptic irrigations [11,13] or of special measures applied to the urethra.[2,6,7] Prophylactic antibiotics probably play no role unless a break in sterile technique occurs.[1,5,19]

Experience with Closed Drainage

Twenty-five consecutive patients in whom closed drainage was maintained for two to three days after transurethral resection of the prostate for benign prostatic hypertrophy were studied by preoperative urinalysis and methylene blue smear and postoperative urine culture with colony count four days to two weeks after removal of the retention catheter. Typed instructions (see box below) were provided for the nursing staff. The results of this study are shown in Chart 2. Of those patients with sterile urine before operation, 75 per cent continued to have sterile urine. The 25 per cent of cases in which the urine became infected included those in which postoperative bladder irrigation was necessary or the closed system was opened unnecessarily.

INSTRUCTIONS TO NURSING STAFF

(To be placed in patient's chart following appropriate written orders.)

Date:____________ Patient:____________

Location:____________

THIS PATIENT'S CATHETER IS TO BE MAINTAINED ASEPTICALLY . . . to prevent cross infection by hospital organisms. This drainage system has been connected sterily in the operating room. Any break in technic will contaminate the patient's bladder.

ORDERS:

(1) Keep *catheter connected to drainage tube.* If irrigation is absolutely necessary because of obstruction, call house officer to perform it aseptically (gloves, sterile towels, scrubbed catheter end, fresh irrigation set up). Never use leg bags or catheter plugs.

(2) Keep *distal end of drainage tube* sterile. Handle aseptically, in sterile collecting bottle or bag. Do not allow end to touch urine in bottle or bag.

(3) Cleanse male meatus daily with Phisohex. Keep catheter taped to leg.

Signed__________________, M.D.

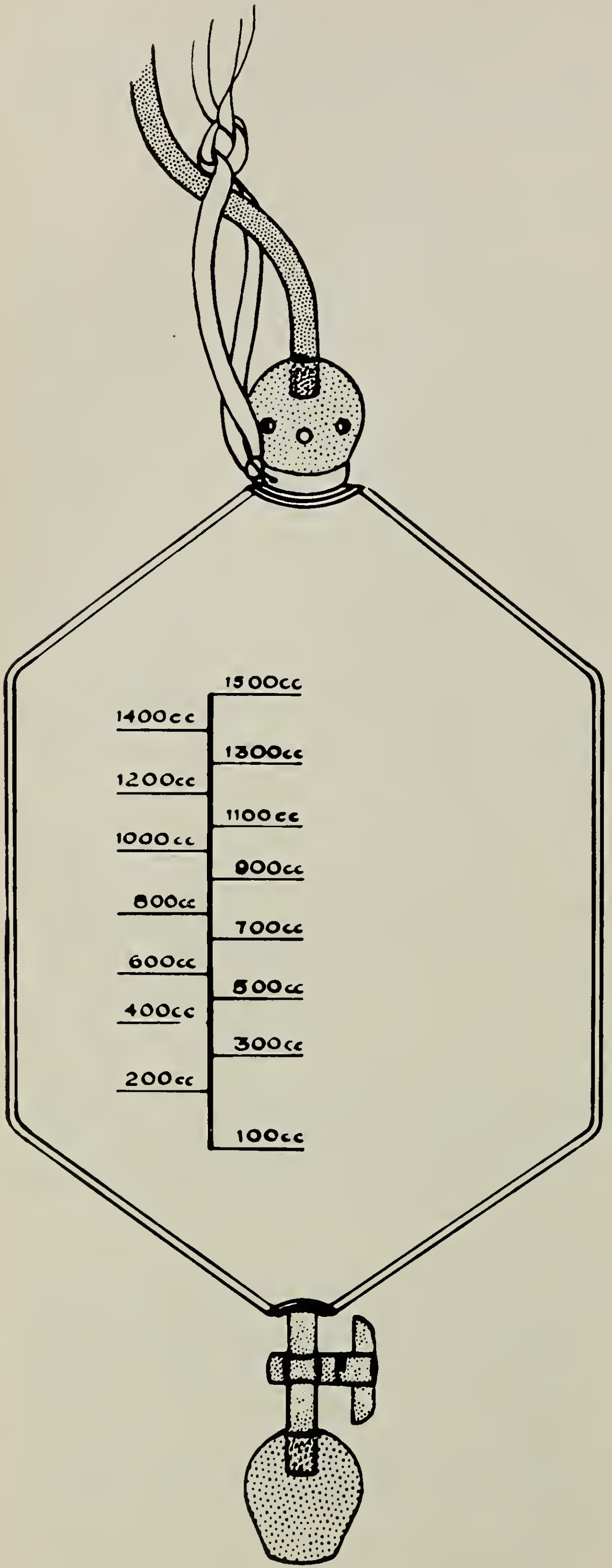

Figure 3.—Proposed aseptic bag system. Note: 1. fixed inlet tubing; 2. drip chamber at inlet; 3. overflow vents; 4. spigot, with drip chamber.

Plan for an Improved Apparatus

A system incorporating the desirable features of the several devices now available with protection from contamination of the emptying mechanism is proposed (Figure 3). It provides the five factors believed essential to asepsis. (It must be pointed out, however, that experimental or clinical proof of the effectiveness of these arrangements has not yet been obtained.) Features of the system are:

1. Fixed tubing. The "cap" cannot be disconnected.

2. An aseptic method of emptying. The spigot lies inside a drip chamber so that contamination, except by air-borne bacteria, is difficult.

3. An anti-reflux device incorporated in the "cap." Vents are provided which let the urine leak out before it can either touch the drainage tube or flow up the lumen of the tube.

4. Free flow, provided by the vents and by the flexible structure of the plastic bag.

5. Portability, assured by the flat shape of the bag and the cotton tapes to tie it to the bed or pin it to the patient's gown. Convenience to the staff is provided by the dependent spigot.

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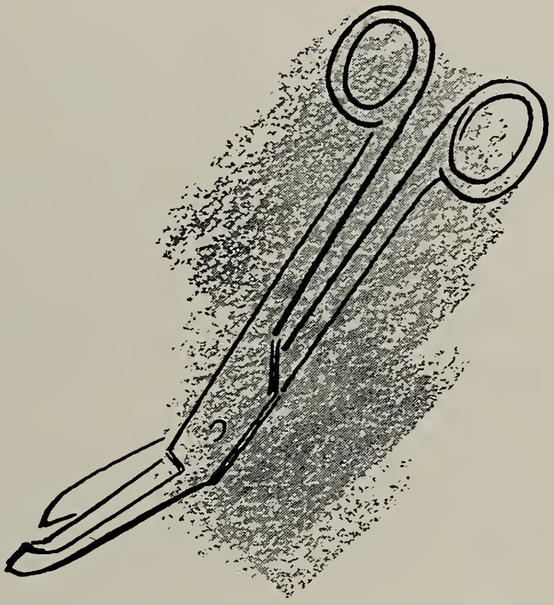

CLINICAL NEUROLOGY

Some Applications of Scanning by Computer

FRANK MORRELL, M.D., *Palo Alto*

■ *The use of averaging techniques permits a great increase in the resolution of time-locked waveforms in the electroencephologram.*

Averaged evoked potentials may be used to study sensory-sensory interactions and the effect of irritative and destructive lesions on the average evoked potential.

More complex computations are possible once averages are derived, as was shown in the application of potential contour mapping, where considerable differences were noted between premature and newborn infants on the one hand and adults on the other.

The flat, low voltage surface potential contour of the neonate was interpreted as reflecting a volume-conducted event having a distant, deep and midline source. Potential contour patterns in the adult were interpreted as showing predominantly neuronally propagated activity arising at the cortical surface.

BY MEANS OF electronic averaging it is now possible to detect evoked responses to sensory stimuli through the intact scalp in human subjects. The technique is basically a form of autocorrelation in which a specified segment of the analog record (electroencephalogram) beginning with a signal trigger is digitized and summed. Activity which is time-locked and phase-locked to the stimulus is thus selectively enhanced at the expense of uncorrelated background rhythms even though the latter may be 10 to 20 times the amplitude of the evoked potential.

Figure 1 illustrates the increased resolution afforded by averaging in the kind of signal-to-noise problem under discussion. In this case, single acoustic or photic stimuli did not produce a discernible alteration in the ongoing electrical activity derived from electrodes placed over the auditory and visual receiving areas in a normal human subject. However, an average of 100 such stimu-

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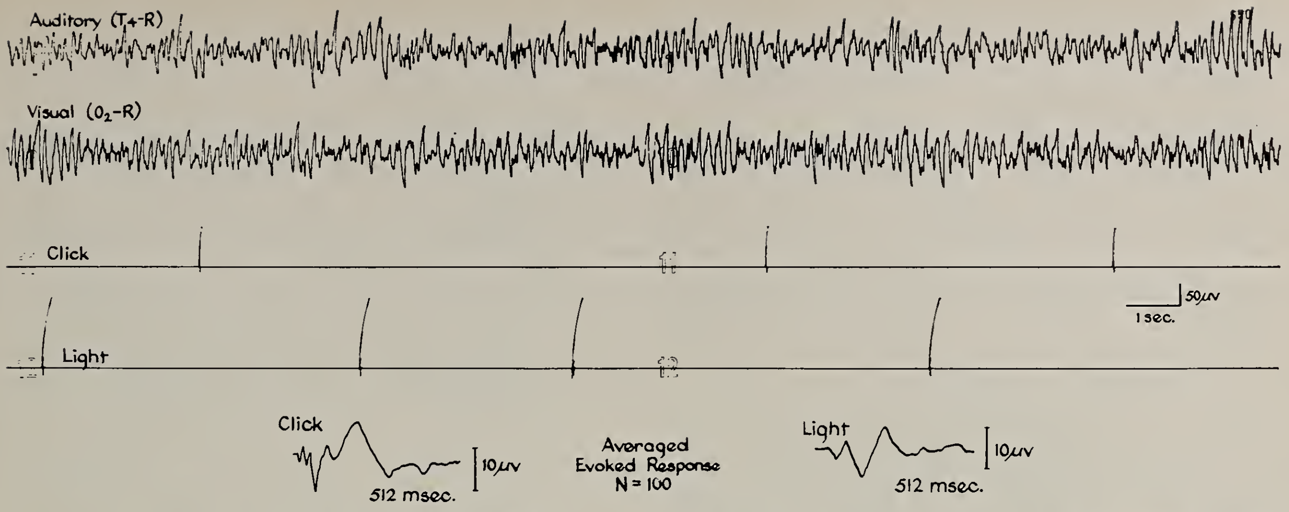

Figure 1.—Electroencephalographic tracings derived from scalp electrodes over auditory and visual areas. Evoked responses to single flash or click stimuli are not detectable in the raw tracing. However, averaging a large number of such responses (in this case 100) reveals a clear time-locked evoked potential.

lations yielded a clear, unequivocal and unique wave-shape identifiable as the cerebral response (from a given electrode site) to each stimulus type.

This, then, is the averaged evoked potential (AEP). With certain limitations related to variability measures, AEP's have the same significance as the single evoked potentials which neurophysiologists have recorded directly from intracerebral electrodes for many years.[1,2,4] The evoked potential is the electrical sign that the brain (or, more strictly, the tissue from which the potential derives) has been perturbed by an externally initiated event. The energy contributed by the external event (in this case, a click or flash of light) acts only upon the sensory receptors. Action potentials recorded from the brain represent energy contributed by the brain and are therefore defined as a *response* to the stimulus. These, of course, are not unitary events. The compound evoked response includes elements reflecting the afferent, incoming volley, elements representing intracortical elaboration and events assignable to efferent, corticofugal discharge. Despite these complexities, the assumption entertained and examined in this paper is that the wave-shape of the evoked potential reflects the manner in which the nervous system processes the information contained in the stimulus.

In the unanesthetized or chloralose-anesthetized animal, neurophysiologists have demonstrated interactions between evoked potentials elicited by different sensory modalities (for review see Buser and coworkers.)[5] These are particularly prominent in non-primary sensory receiving areas. Some of our own observations on sensory-sensory interactions in man will be discussed first.

With averaging techniques, particularly, responses to stimuli of any sensory modality may be

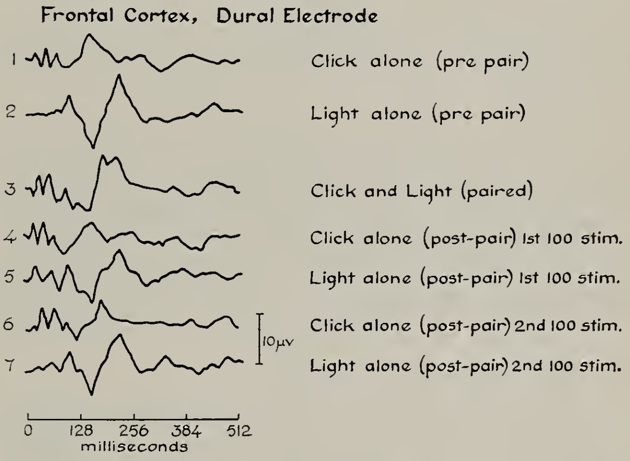

Figure 2.—Contingent interaction. Each trace is an average of 100 randomly scheduled stimulations, first of a click alone (1), next of a light alone (2), and of click and light paired (3), such that the subject perceives them as simultaneous. After pairing, the click alone was again presented 100 times (4), the average showing no substantial difference from that of the control (1). Following this, 100 stimulations of light alone were averaged and in this case the resultant evoked potential (5) revealed early components which resembled those of the click-evoked potential and were not apparent in the photic evoked potential averaged prior to paired stimulation (2). Thereafter another sequence of click alone and light alone were presented. The averaged photic evoked potential for the second 100 stimulations revealed much less of a resemblance to the auditory response. All potentials were derived from an implanted extradural electrode in the left mid-frontal region. The reference electrode was on the left ear lobe. No motor response was required to any of these stimuli.

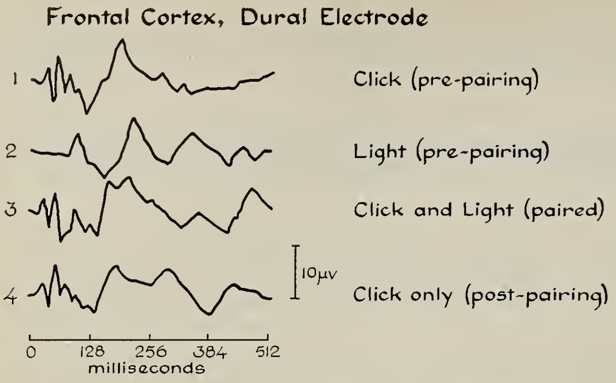

Figure 3.—Contingent interaction. Same patient and same electrode as in Figure 2 but another recording session. In this instance the click and light stimulation were randomly intermixed during the pre-pairing interval. Stimuli for each modality were retrieved and averaged separately (1 and 2). This was followed by 100 trials of paired (simultaneously presented) click and light stimulation. Following this, 100 trials of click alone were presented (4). The averaged evoked response for the latter reveals late components having a striking resemblance to the light-evoked potential which were not apparent in the click-evoked response before the pairing. In this experiment the patient was instructed to count all stimuli regardless of modality and to press a key for every tenth stimulation.

recorded from many areas in the brain. In the frontal cortex, for instance, some particularly interesting interactions have been noted between potentials elicited by click stimuli and those elicited by light.

Figure 2 demonstrates averaged tracings obtained from an implanted epidural electrode under each of the conditions listed. The patient required implantation of a sheaf of electrodes for diagnostic and therapeutic purposes. He had an epileptogenic lesion although the epileptic discharge did not happen to involve the area from which this particular electrode derived.

It is especially noteworthy that the configuration of the response to click was quite different from that to light. When the two stimuli were paired (time relationships adjusted so that the subject perceived them as simultaneous) the averaged compound response reflected both sensory influences. Immediately after pairing, however, the response to single stimuli was altered from that which obtained before the pairing. Light alone, when presented immediately after pairing (Figure 2, line 5) elicited an early component having a much greater resemblance to click-induced activity than anything produced by light before the pairing (Figure 2, line 2). The effect was transitory and began to disappear during the second hundred stimulations (Figure 2, line 7).

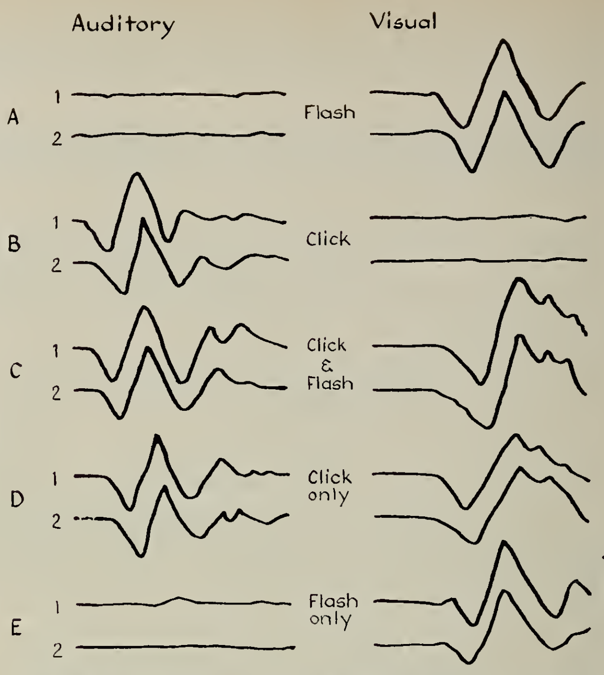

Figure 4.—Evoked potential interactions. Normal subject with scalp electrodes. (Full explanation in text.) Calibration: 10*µ* volts. Analysis time: 125 milliseconds. Each trace represents the average of 100 stimulations. Auditory area defined as T_5-R, visual area as 0_1-R. Reference (R) was the Goldman electrode using 22 positions of the 10-20 system.

Another experiment with the same person and using the same electrode illustrates the reverse effect in which the click-induced response (post-pair, Figure 3, line 4) contains late components evident in the light response (pre-pair, Figure 3, line 2) but not elicited by click at all before pairing (Figure 3, line 1).

In some normal subjects, using scalp derivations and just liminal stimuli, there was little or no early response to flash over auditory cortex (Figure 4, A). Conversely, the faint click induced no occipital-evoked potential (Figure 4, B). Averages emerging from paired stimulation (Figure 4, C) were seen in both cerebral zones and had a more complex form than might be expected from simple linear summation of the two signals. Following the paired trials, the click alone elicited a response in visual cortex similar in form to that produced in the paired interaction (Figure 4, D). Although again transitory, this effect persisted for 200 trials. On the other hand, the flash alone did not elicit a corresponding response in auditory cortex (Figure 4, E).

In another normal subject a more extended series of trials (400) was carried out under each stimulus condition (Figure 5). Following the

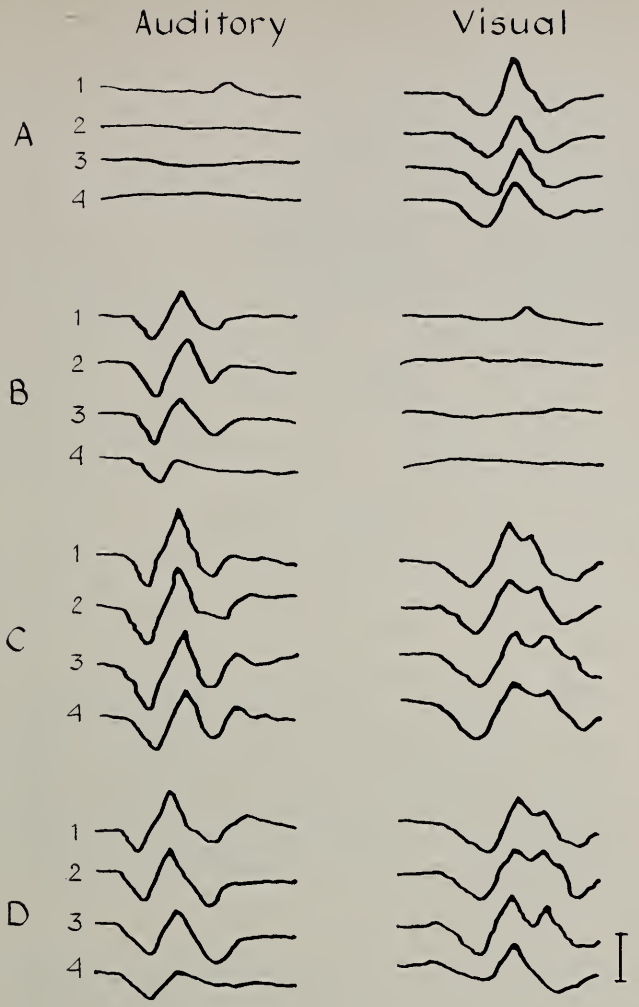

Figure 5.—Similar experiment (to that in Figure 4) on a normal subject in which four successive averages of 100 were obtained for each condition. (Further explanation in text.) A: photic stimulus, B: acoustic stimulus, C: paired stimulation (click and flash), D: click alone post-pairing. Voltage calibration: 10μ volts. Analysis time: 125 milliseconds. Each trace represents the average of 100 stimulations. Auditory electrode was T_5-R, visual electrode was 0_1-R. Reference (R) was the Goldman electrode using 22 positions of the 10-20 system. Note the decay of the click-evoked response in both visual and auditory areas post-pairing.

paired trials (Figure 5, C) the decay of the click-evoked occipital response (Figure 5, D) may be seen quite clearly. The successive averages of 100 stimulations each afford some indication of the reliability of these measures, as well as illustrating graphically how transitory changes might be washed out if inappropriately large numbers of trials had been averaged together.

These interactions are extremely sensitive to the presence of both irritative and destructive central nervous system lesions. Although it is far too early to formulate general rules about effects of various lesions, we have obtained consistent results in three patients having in common irritative, epileptogenic lesions of auditory cortex. The inference that auditory cortex was involved did not rest solely upon the finding of temporal lobe spike discharge but was corroborated by clinical evidence of altered auditory perception during ictal episodes.

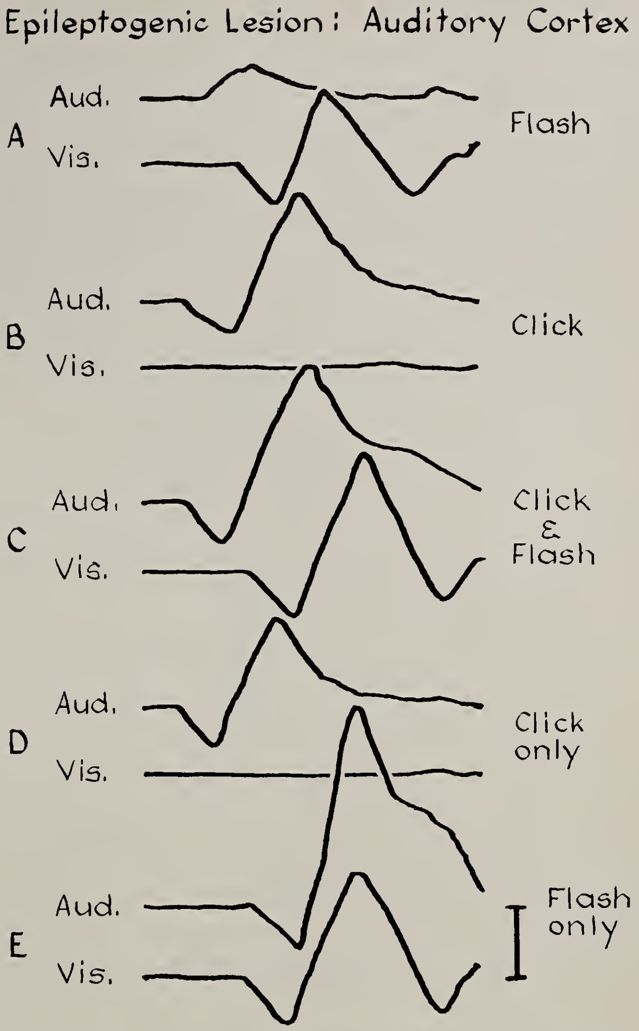

Figure 6.—Evoked potential interactions in a patient with an epileptogenic lesion involving the right auditory cortex. Auditory area is T_6-R, visual area is 0_2-R. Reference (R) was the Goldman electrode using 22 positions of the 10-20 system. Each trace is the average of 120 stimulations. Calibration: 10μ volts. Analysis time: 125 milliseconds.

Figure 6 shows that before the paired trials, the light stimulus produced an evoked response in both auditory and visual areas (Figure 6, A), whereas the click elicited a response only in the auditory cortex (Figure 6, B). Again following 100 paired trials, the click or light separately were presented. Click produced no alteration in visual cortex while light elicited an augmented response

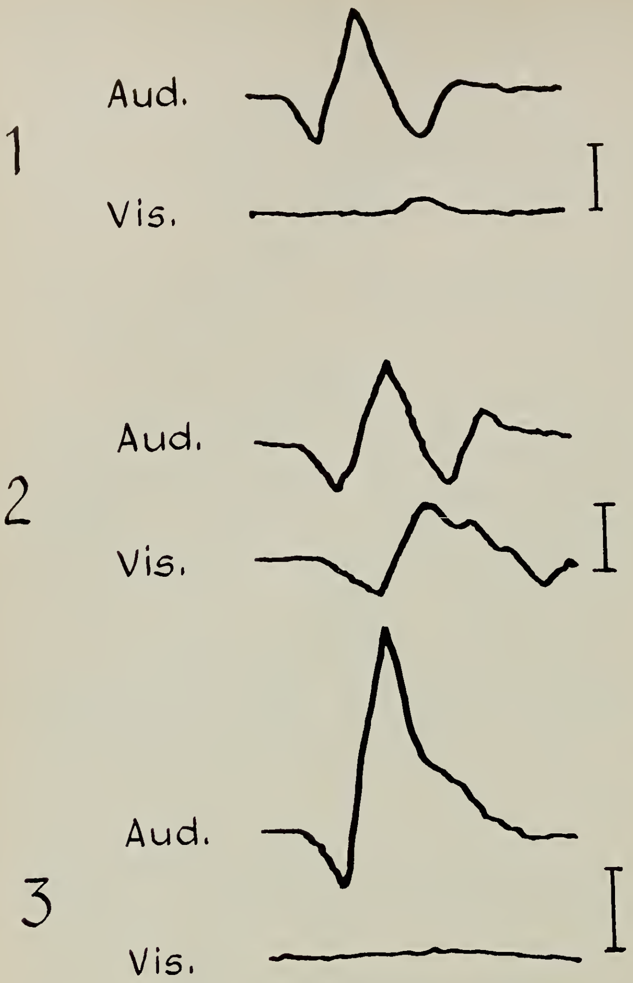

Figure 7.—Evoked potential interactions in a patient with a left temporal epileptogenic lesion. Auditory area: T_5-R, visual area: 0_1-R. Reference (R): Goldman electrode. Each trace was the average of 256 stimulations. 1: evoked responses to click only delivered prior to paired trials. 2: evoked responses to click and flash paired. 3: responses to click alone post-pairing. Calibration: 10μ volts. Analysis time: 125 milliseconds.

over auditory cortex. The pattern therefore is opposite to that found in the normal subject.

A second patient (Figure 7) had essentially the same changes. In the third patient with ictal alteration of sound perception, in which the lesion was known to be limited to the left hemisphere, it was possible to obtain bilateral recording from auditory and visual areas. In this situation the post-pair flash stimulus (Figure 8, D) elicited an augmented evoked potential only in the cortex containing a lesion and not in the normal right side. The interaction on the right, recorded simultaneously, revealed a normal pattern (Figure 8, C and D).

These findings are consistent with previous observations[8,9] on experimental epilepsy in animals. Epileptic tissue is more than normally responsive to stimulation via any sensory modality. Yet, once activated, the epileptic area seems unable to participate in normal transactional processes as expressed in the capacity to form temporary connections with other functional systems.

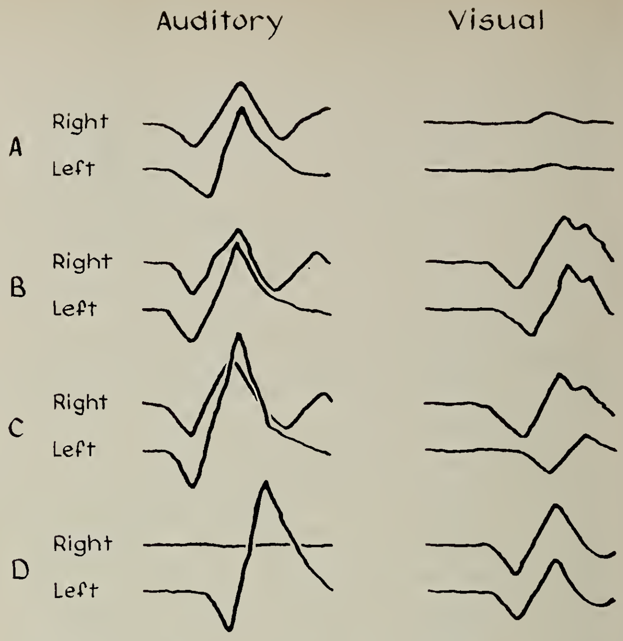

Figure 8.—A third patient with unilateral epileptic focus involving left auditory cortex. (Full explanation in text.) A: click (pre-pair), B: paired stimulation, C: click alone (post-pairing), D: flash only (post-pairing). Analysis time: 125 milliseconds. Each trace is an average of 100 stimulations. For the auditory area, electrodes T_6 (right) and T_5 (left) were used and for the visual area, electrodes 0_2 (right) and 0_1 (left) were used. Reference (R) was the Goldman electrode.

Thus far we have dealt with only the simplest and most basic application of computer technology. But once these stimulus-related events have been discriminated from background "noise" and clearly visualized, they can then be used as a basis for further, more sophisticated computation.

For example, one may inquire into the spatial or topographic attributes of the AEP. As every electroencephalographer knows, the spatial distribution of abnormal electrical transients provides important clues for locating the source of the disturbance. In general, the deeper the source the wider the surface distribution of a given electrical event. Potential contour maps may be constructed[3] from which the depth of origin of a particular discharge may be calculated. However, the accuracy of the calculation is compromised not only by

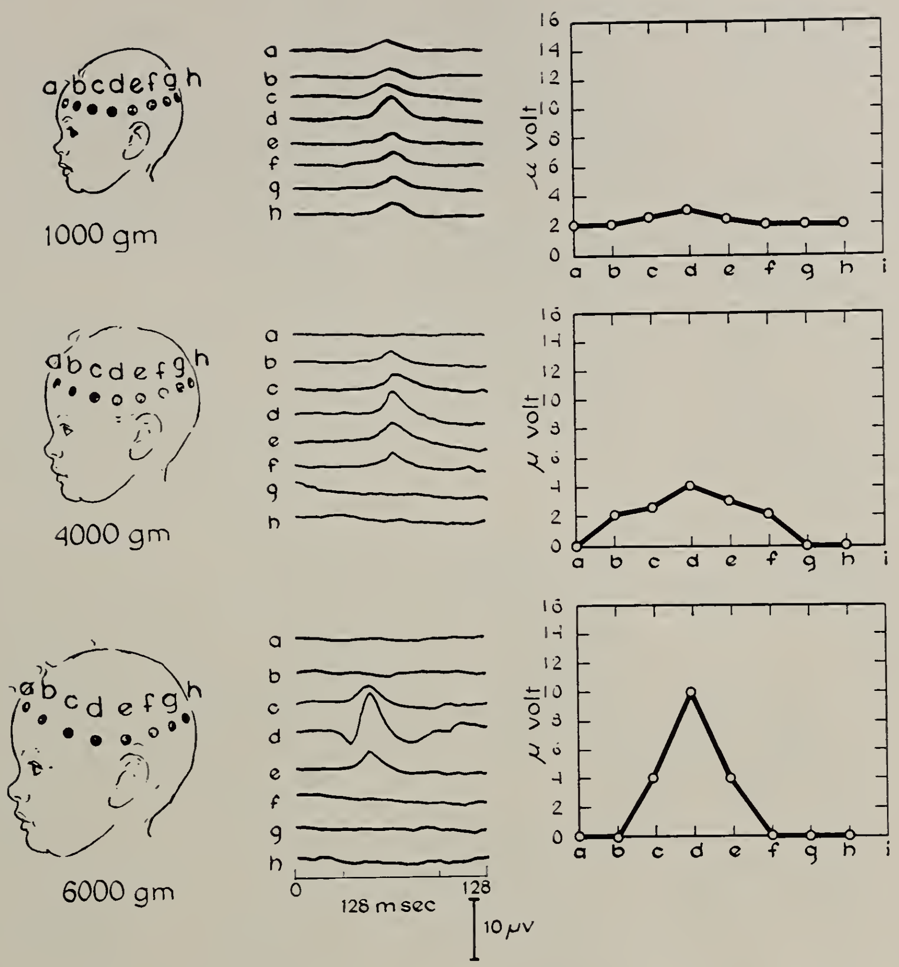

Figure 9.—Spatial distribution of averaged acoustic evoked potentials, anterior-posterior array, in premature and newborn infants. Each trace is the average of 100 stimulations.

boundary conditions and inhomogeneity of the medium, but also by the difficulty of distinguishing the identical event in all areas when it is both immersed in competing background rhythms and distorted by the effects of neuronally propagated activity.

Computer techniques which enhance time-locked events at the expense of unrelated background rhythms are ideally suited for application of contour mapping to evoked potential waveshapes. Availability of multichannel magnetic tape recording made it possible to sample a sufficiently large number of areas simultaneously so as to obtain adequate data points for a given plane of derivation. Both light and acoustic (barely audible click) stimuli were used but we shall limit this discussion to the click-evoked response.

When the computer had produced a set of averaged waveforms, a cross-correlation analysis between each member of the set and every other member was undertaken. The cross-correlation provided a measure of coherence among the set of wave-shapes to verify that they all represented the same electrical event as "seen" from different locations (or, on the other hand, quantitative evidence for differences within the set).

If the cross-correlation was sufficiently high (any criterion can be chosen; 90 per cent coherence was used here) for all comparisons, the computer calculated the maximum difference between positive and negative values in each trace and displayed the result graphically for each electrode location.

This technique has now been applied in a num-

Maturation

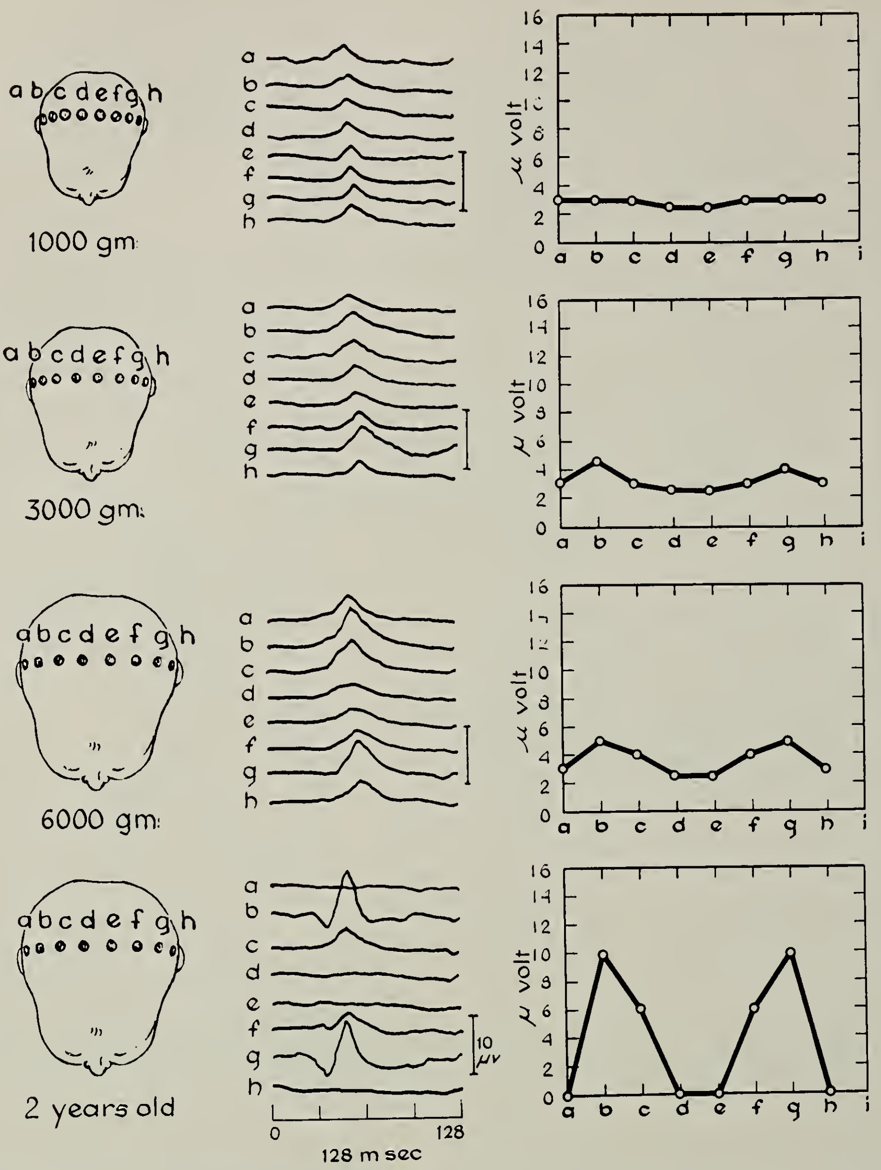

Figure 10.—Spatial distribution of averaged acoustic evoked potentials, transverse array. Note the pattern of maturation. Each trace is an average of 100 stimulations.

ber of studies. Among the most interesting findings was the evidence for a maturational change in potential contour patterns.

Figure 9 illustrates the developmental changes observed in the click-evoked potential contour beginning with the premature infant (birth weight 1,000 gm). The pattern is even more dramatic when the electrodes are arranged in transverse perspective (Figure 10). The double peaked contour of the two-year-old approaches that of the normal adult subjects shown in Figure 11. It must be noted that the analysis time for the adult was 256 milliseconds as compared with 128 milliseconds in the infants and children. However, the maps are comparable, since only the trough-to-peak amplitude of the first early component was used for construction of that for the adult. It is interesting that in the anterior-posterior electrode arrays (second and third sections of Figure 11) the potential peak for the adult was somewhat more posterior than the corresponding peak in the infant (third section of Figure 9), suggesting that with growth there occurs a shift in the relationship of brain to skull landmarks resulting in apparent backward migration of auditory cortex.

The major difference between the adult and the

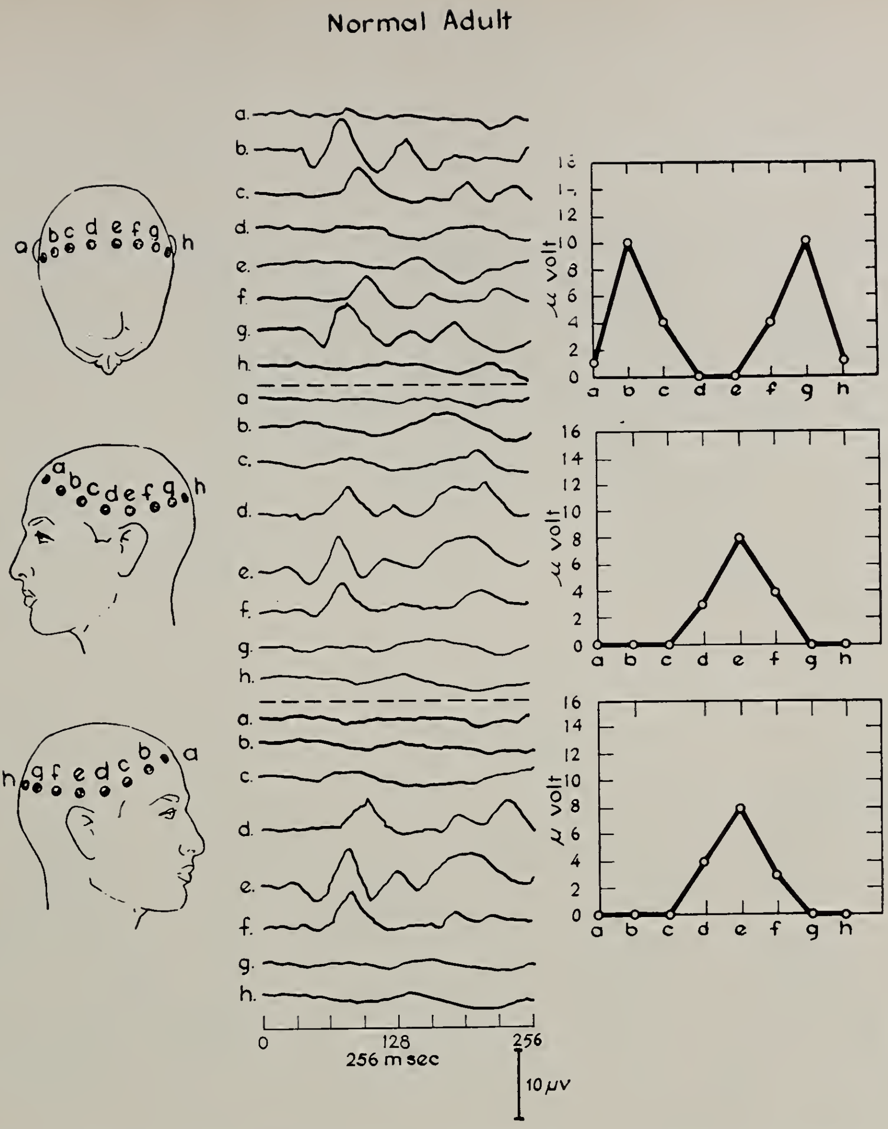

Figure 11.—Spatial distribution of averaged evoked potentials in the normal adult. Acoustic stimulation. The potential contour maps were based upon plotting the trough-to-peak amplitude of the first major deflection.

premature or newborn infant in this study was the flat surface potential contour of the latter as contrasted with the pronounced peak of much higher amplitude characteristic of the adult. The tracings presented are typical ones, representative, respectively, of 11 premature infants between 1,000 and 1,500 gm, 18 newborn infants (3,000 to 4,000 gm) and 22 young adults. A more detailed analysis of these data will be presented in another communication.

The implication of the contour pattern in the premature and newborn child is that activity reaches all electrodes at the same time and with approximately the same amplitude. We interpret this as indicating a volume-conducted event arising from a distant, deep and midline source. A biologically appropriate generator would be the medial geniculate nucleus of the thalamus. An alternative interpretation is possible within the physical constraints of the data. One need not assume a single source for the potential. It is theoretically possible that similar and simultaneous potentials occur at all cortical loci subjacent to the recording electrodes. This latter seems a less likely alternative since there is no known neural pathway having exactly the required properties (especially one which is present at birth and obligingly disappears during maturation).

In contrast, the pattern observed in the adult and older child suggests that the potential arises in the auditory and para-auditory cortex of each hemisphere.

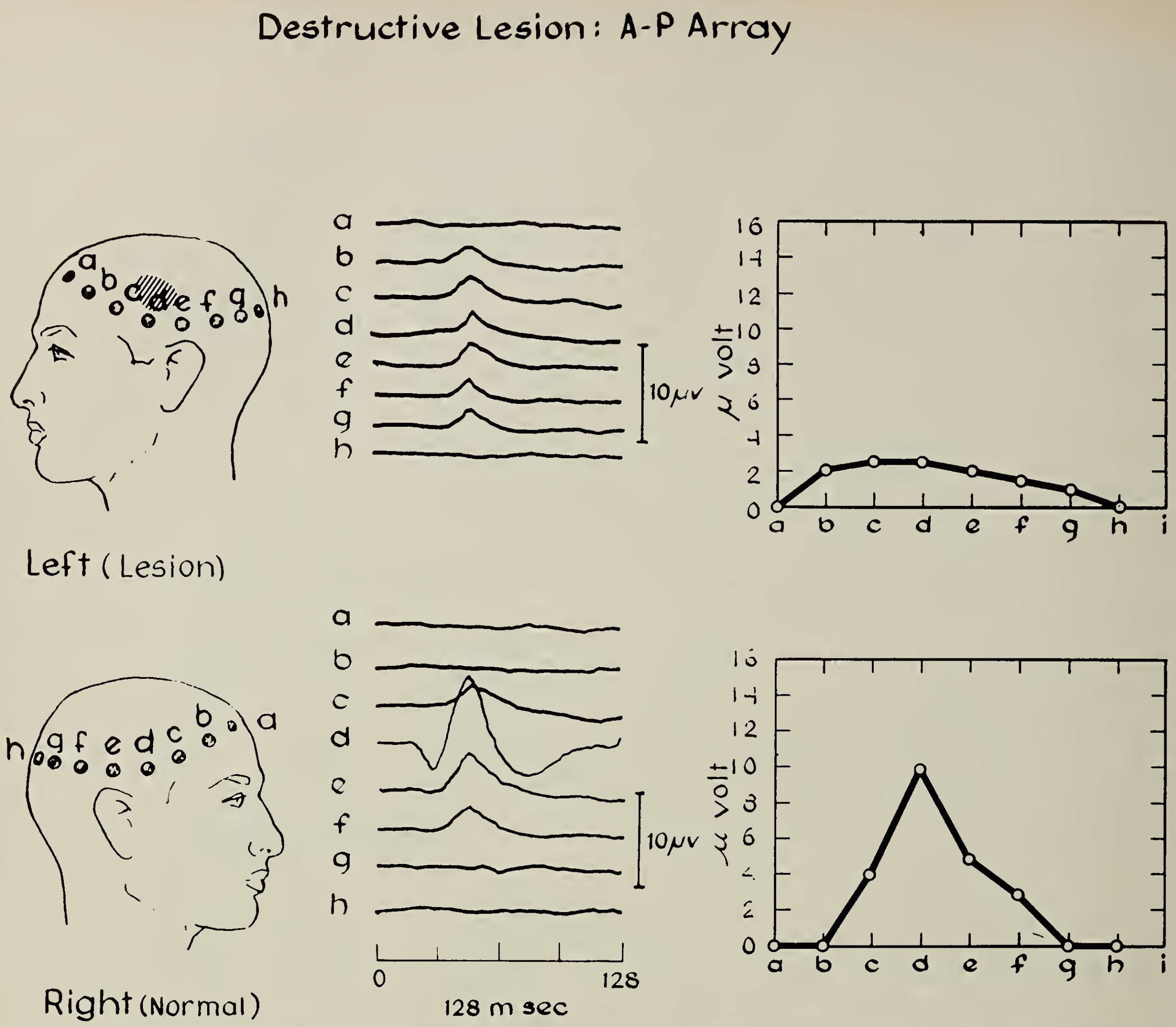

Figure 12.—Averaged acoustic evoked potentials and graphs of evoked potential contours from each hemisphere in a patient with a large destructive lesion involving the left auditory cortex. Note the similarity of the contour map on the left to that of the premature and newborn infants.

A corollary of these findings is that, at least for the auditory system, thalamo-cortical interactions do not occur normally until several months after birth. It is of considerable interest in this connection that the developmental pattern shown here is one which closely parallels the gradual myelinization of human thalamo-cortical radiation fibers.[6] Thus, if the foregoing interpretation is proved correct, the spatial distribution of an averaged evoked potential would provide a sensitive index of the maturation of thalamo-cortical interconnections.

Support for this interpretation is provided by an analysis of several clinical cases studied early in our work. Figure 12 demonstrates the contour pattern obtained from a patient with a large destructive glioblastoma involving the entire left temporal lobe. The averaged acoustic evoked potentials are seen in the center of the figure and the surface potential contour maps (anterior-posterior arrays) are seen on the right side with the side of the lesion above and the normal hemisphere below. Over the hemisphere with the lesion the contour had a flattened configuration and lower overall amplitude highly reminiscent of that seen in the premature and newborn child (Figure 9). This is the pattern expected when cerebral cortex is absent or non-functional.

On the other hand, purely irritative lesions may produce an exaggerated AEP as noted previously (Figures 6, 7, 8). The potential contour for one such patient is illustrated in Figure 13. A comparison between contour maps (transverse arrays) for destructive and irritative lesions is given in Figure 14.

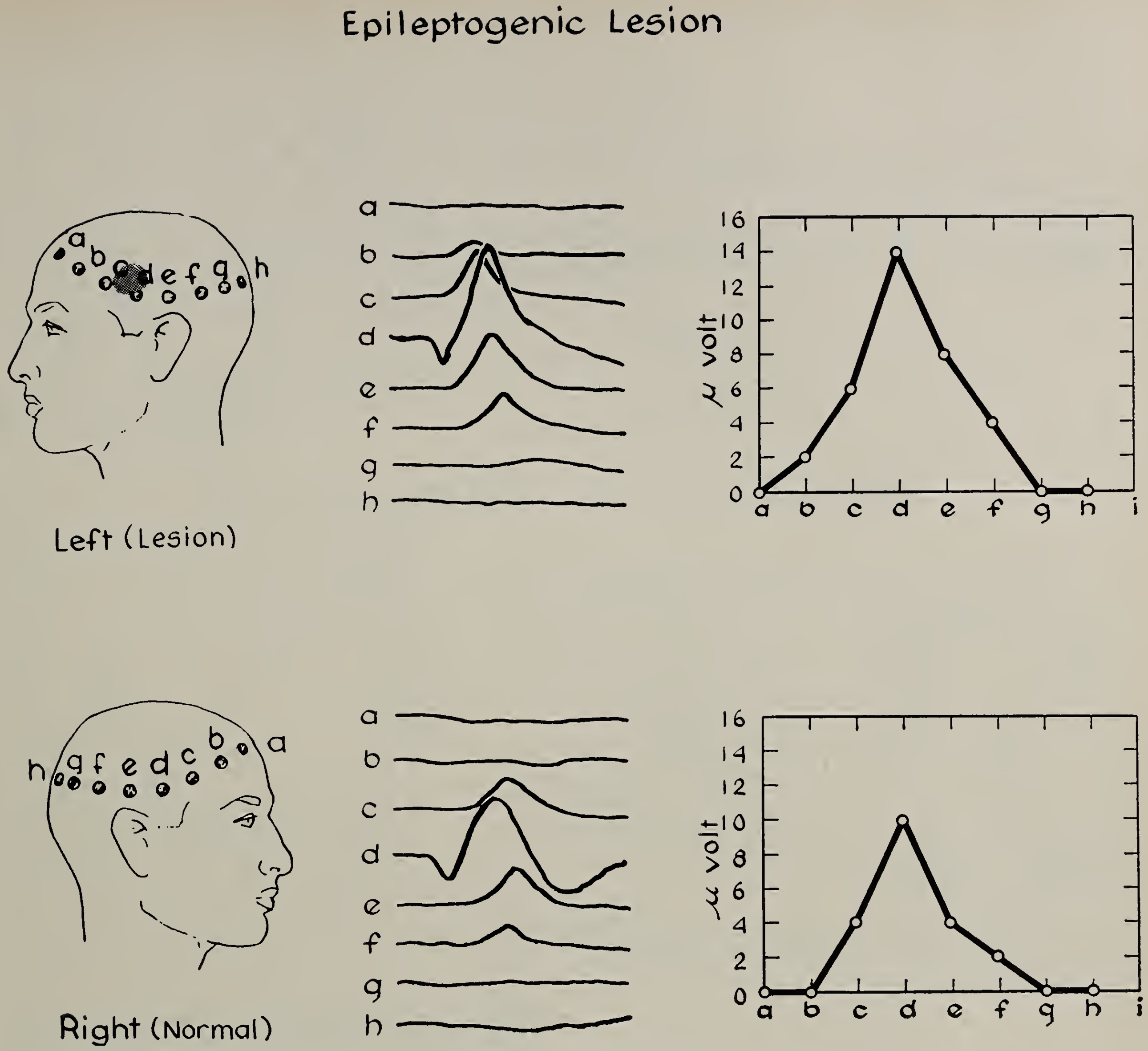

Figure 13.—Averaged acoustic evoked potentials and graphs of evoked potential contours from each hemisphere in a patient with an irritative lesion of the left hemisphere (auditory cortex). Calibration as in Figure 12.

Again, we wish to emphasize that these are individual examples and not to be construed as providing general rules. Many patients have combined destructive and irritative lesions which would nullify or at least obliterate the clarity of this distinction. Nevertheless our observations on destructive lesions are in accord with those of Vaughan and coworkers[10,11] for the visual system. With respect to irritative lesions, Gastaut[7] has shown augmented AEP's in the visual system.

Our purpose has been to document in a variety of ways the use of computer technology in clinical neurology. We have shown the usefulness of the potential contour technique in analysis of maturation and development. Sensory-sensory interactions disclosed by AEP's may be sensitive to very subtle or minimal perturbations of cerebral function especially those functions concerned with information transfer and storage.

We are reasonably confident that the analysis of stimulus-locked potential changes now made possible through application of computer technology will ultimately reveal many intimate details of the manner in which the nervous system processes information. In a preliminary way the data outlined above suggests that these techniques may also provide insight into the mechanisms by which central nervous system lesions interfere with these processes.

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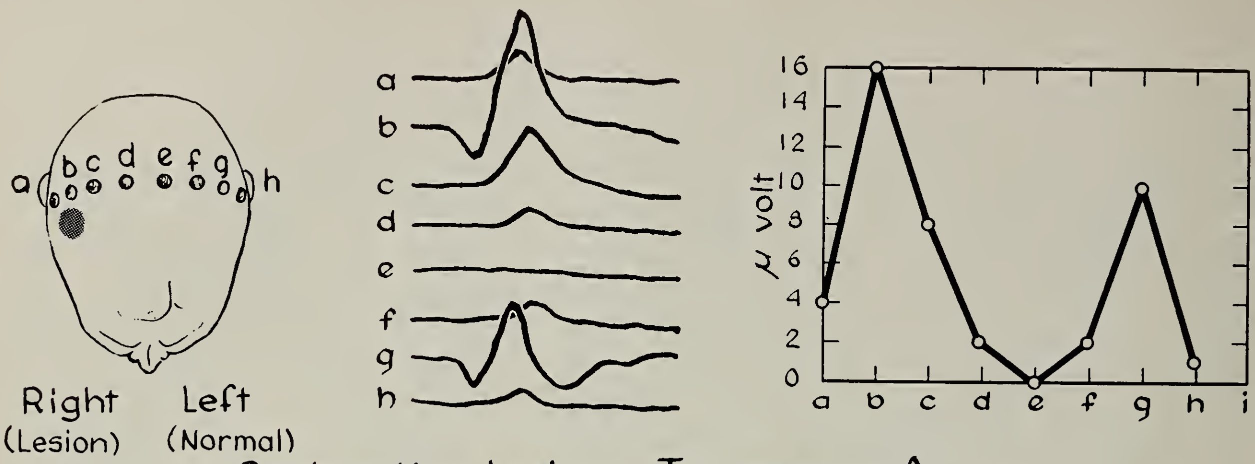
Epileptogenic Lesion: Transverse Array

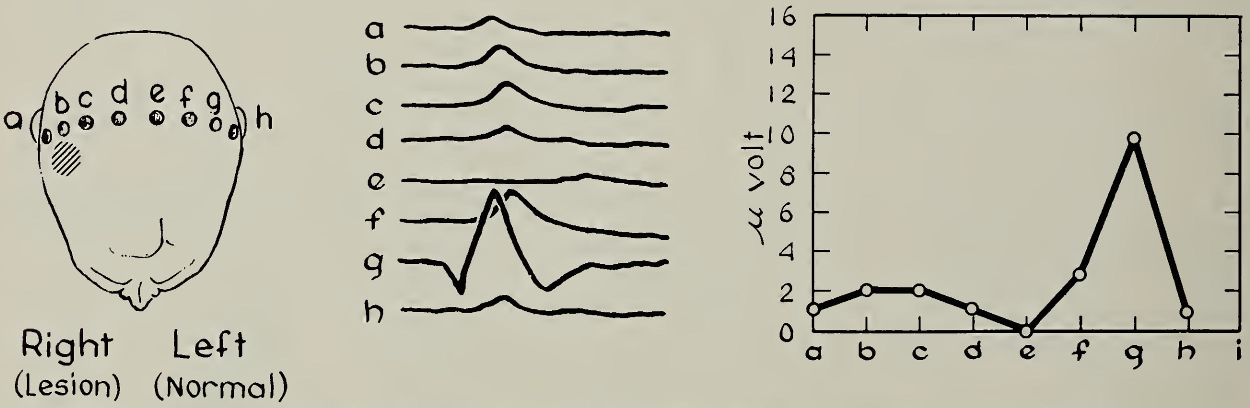
Destructive Lesion: Transverse Array

Figure 14.—Comparison of evoked potential contours (transverse array) in the case of destructive (below) and irritative (above) lesions. Calibration as in Figure 12.

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Mortality in Spinal Cord Injuries

Follow-up Report

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Long Beach

■ *The principal cause among 137 deaths in a series of 1,613 patients with traumatic spinal cord lesions treated at Veterans Administration Hospital, Long Beach, was renal disease attributable to the paralysis of the bladder and bladder sphincter and resultant genito-urinary tract infections. The second ranking cause was pulmonary disease. Before 1960 no deaths from cancer had occurred in this series, but between 1960 and 1962 three patients died of carcinoma of the bladder. It can be expected that as these patients reach higher age groups the incidence of neoplasms will increase.*

THIS COMMUNICATION is a follow-up report on mortality of patients with spinal cord injuries up to 1 July 1962. It is complementary to the first preliminary report covering the period from 1 April 1946 to 1 October 1960.

The admissions to the Spinal Cord Injury Center, Veterans Administration Hospital, Long Beach, California are shown on Chart 1. This commences with the initial group of 180 patients on 1 April 1946, shows the increase each year as of the first of January and ends at 1 July 1962.

Chart 1 shows that the rate of admissions has followed a linear increase each year. Up to 1 July 1962 there had been a total of 1,759 admissions —1,613 patients with traumatic and 146 with non-traumatic lesions.

During the 16 years and three months covered by this report there was a total of 236 deaths among the total 1,759 patients, an over-all uncorrected mortality rate of 13.42 per cent. As of 1 October 1960 the over-all uncorrected death rate was less, 11.32 per cent—184 deaths in 1,626 admissions.

Chart 2 shows the total number of deaths annually from 1946 to 1962 and also shows the total number of deaths attributed to uremia for each corresponding period. This aspect will be studied further in order to show the corrected number of deaths of patients with traumatic lesions—that is, directly or indirectly related to the original trauma. The number of deaths due to eventual uremia

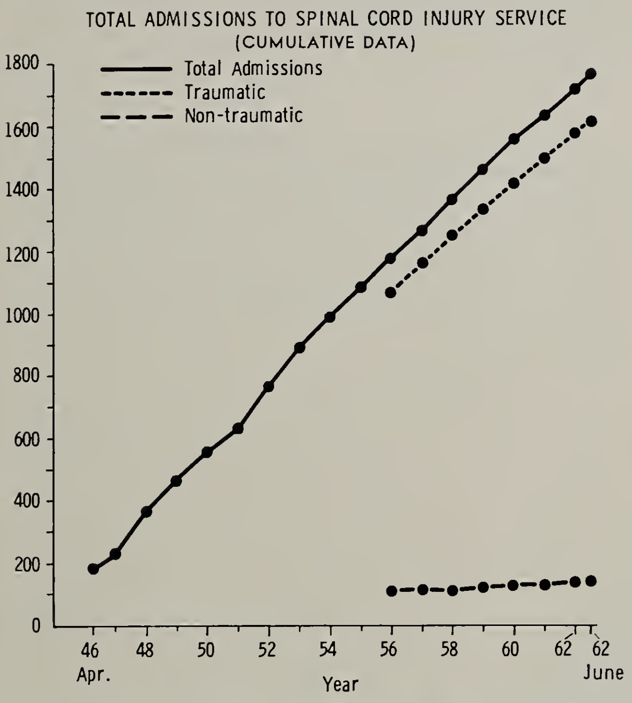

Chart 1.—Cumulative total admissions, patients with traumatic and non-traumatic lesions, from 1 April 1946 to 1 July 1962. Annual data as of 1 January 1947 to 1 January 1962.

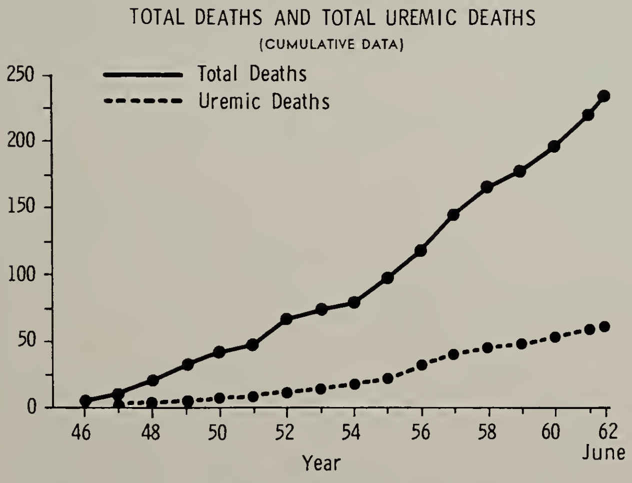

Chart 2.—Cumulative totals of deaths among all patients, those with traumatic and non-traumatic lesions, from 1946 to 1962, with the number of deaths due to uremia shown separately. Annual data as of 1 January 1947 to 1 January 1962.

From the Physical Medicine and Rehabilitation Section, Spinal Cord Injury Service, Veterans Administration Hospital, Long Beach, and the Department of Physical Medicine and Rehabilitation, University of California School of Medicine, Los Angeles.

Presented before the Section on Physical Medicine at the 94th Annual Meeting of the California Medical Association, San Francisco, 28 to 31 March 1965.

from chronic renal infection including amyloidosis is shown in Chart 2. An uptrend in deaths in both categories began in 1955 and 1956 and has continued since then. Through 1955 there were 22 deaths due to uremia and the total of such deaths now has reached 62. The combined total of deaths to the time of this report is 236. Through 1954 there were 80 deaths and the direction of the curve rose more steeply to 146 in 1957. Since 1957, the line has followed a more linear increase.

The number of living patients from 1 April 1946 to 1 July 1962 is shown on Chart 3.

Chart 4 depicts two uncorrected curves—the upper curve showing the annual percentage of survivors and the lower curve the percentage of deaths.

Chart 5 shows the uncorrected percentage of renal deaths in the total deaths annually. Since 1956 the percentage of renal deaths among the total deaths as shown on the chart has remained between 26 per cent and 29 per cent. Hence, the increase in the over-all uncorrected death rate from 1 October 1960 to 1 July 1962 is apparently not due to any increase in renal deaths. In the future, other frequent causes such as pulmonary disease, suicide, secondary amyloidosis, liver disease, peritonitis and hemorrhage will be studied.

From 1 October 1960 to 1 July 1962 there were 37 deaths, 33 among the patients with traumatic lesions and four among the non-traumatic. In the traumatic group the main causes of death were: renal, 8; cardiac, 4; pulmonary, 5; suicide, 3; cancer of bladder, 3; secondary amyloidosis, 2; arteriosclerosis, 2 and one each due to skull fracture with hemorrhage, automobile accident, sensitivity to intracaine, cirrhosis of liver, leukemia and "cause unknown."

The four deaths in the non-traumatic group were due to: uremia, pneumonia, cancer of the lung, and syringomyelia.

Discussion

Renal disease was the leading cause of death in this group of patients. Paralysis, infection, obstruction, and secondary renal amyloidosis were

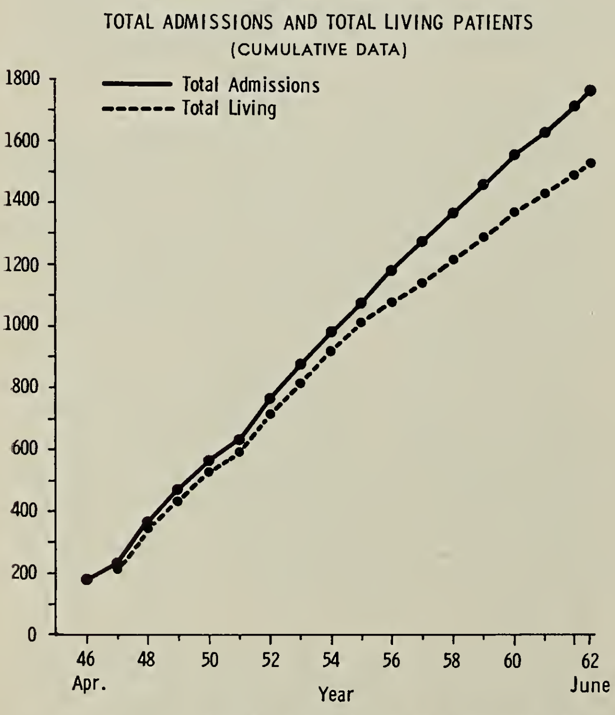

Chart 3.—Cumulative numbers of admissions (as in Chart 1) and the total of living patients as of 1 January each year from 1947 to 1962.

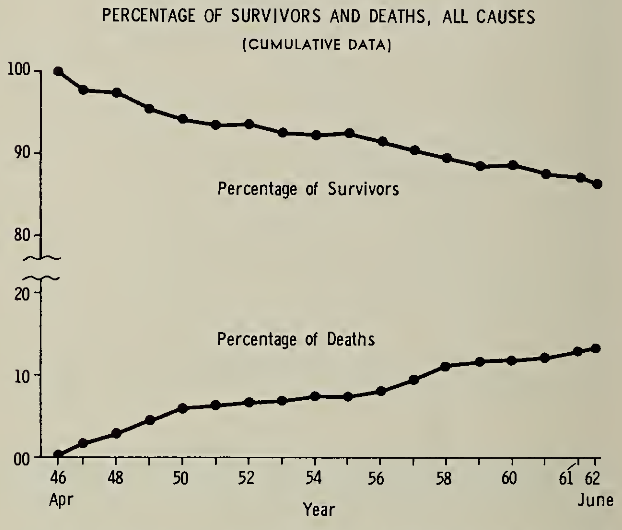

Chart 4.—Cumulative data on percentage of survivors and of deaths from all causes, uncorrected, annually from 1946 to 1962. Annual data as of 1 January 1947 to 1 January 1962.

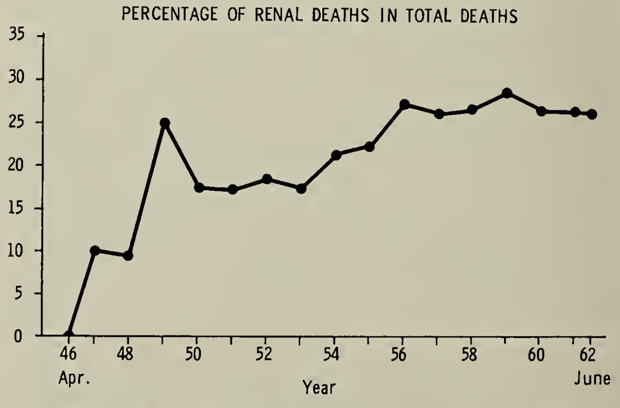

Chart 5.—The uncorrected percentage of renal deaths in the total deaths annually. Annual data as of 1 January 1947 to 1 January 1962.

contributing factors. Improvements in combating these factors can be expected.

Pulmonary causes are second. In this cause, impaired pulmonary function is a contributing factor and improvements in treating this may reduce mortality.

Much work is being done in psychiatric and psychological fields and reductions in suicidal deaths are hoped for.

Precautions to keep decubitus ulcers from developing, or prompt treatment of them when they do develop, thereby preventing osteomyelitis, will gradually reduce the main cause of secondary amyloidosis.

As the paraplegic population approaches the same age group proportions as apply to the rest of the State of California, it can be expected that deaths due to cancer and to cardiovascular causes will increase and approach the same rates as apply to the rest of the population. It should be noted that this report includes three deaths from carcinoma of the bladder. This was not a listed cause in the previous preliminary report.

In the combined total of 104 deaths listed in the preceding preliminary report and the 33 deaths from traumatic spinal lesions listed in this follow-up report the causes and the proportion of each cause in the total is as follows:

	No. of Deaths	*Per Cent of Total*
Renal	57	41.6
Pulmonary	20	14.6
Suicide	17	12.4
Amyloidosis, secondary	9	6.6
Peritonitis	6	4.4
Cardiac	4	2.9
Hepatitis, acute	4	2.9
Carcinoma, bladder	3	2.2
Embolism, pulmonary	3	2.2
Cirrhosis	2	1.5
Miscellaneous (one of each)	12	8.7
Total	137	100.0

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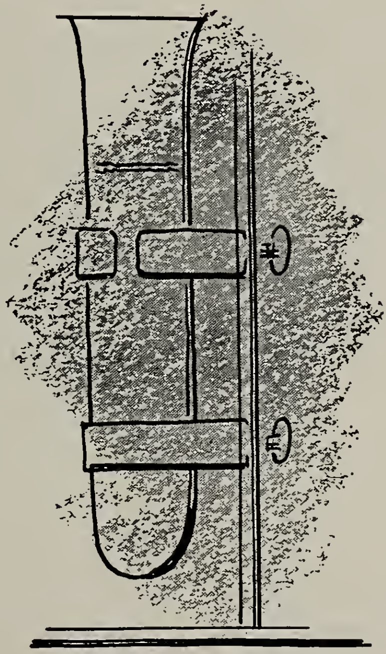

In Defense of the Obstetrician and Obstetrics

RALPH L. HOFFMAN, M.D., *San Diego*

■ *Changes and advances in obstetrics are emphasized by the comparative study of private and one hospital practice in 1939 and 1964. Education, prenatal care, anesthesia, antibiotics, transfusions have all been instrumental. Old problems—abortion, toxemia, prematurity, developmental abnormalities—remain with us. New developments, both professional and economic, some not desirable, face us and demand that active practicing obstetricians take an active role in helping direct their course.*

IT IS WELL to remember that obstetrics as we know it has a rather short history. The first obstetrical lectures I attended, in 1930, were presented by Dr. Reuben Peterson, a pioneer obstetrician at the University of Michigan. To recall the names of a few of those active in teaching at that time is to recite a list of giants among the founders of our profession: Williams, De Lee, Polak, Jeff Miller, Beck and San Francisco's own Frank Lynch. The bases of our specialty laid by such men as these have been firm foundations on which others have built our rapidly developing and changing practice.

To review these changes points up the differences between our former procedures and today's, and at the same time calls attention to the accelerating accumulation of knowledge and its effect on our thinking. Such a review also indicates where we are heading. To make these comparisons more specific, I have chosen to compare some present-day facts with those in a study I presented before the staff of San Diego's Mercy Hospital in 1940.

Gross maternal mortality rates portray most dramatically one change in obstetrics. The rate had been above 60 per 10,000 live births until the early 1930's. In 1938 it was 43.5. The rate in 1963 (the latest year for which data were available) was 3.7. In San Diego County, it was 29.0 in 1939, 3.5 in 1963. At Mercy Hospital it was 15.0 in 1939, 3.4 in 1964.

Neonatal mortality rates also depict great improvement. The national rate was 29.3 per 1,000 live births in 1939. In San Diego County it was 34.2 per 1,000; at Mercy Hospital 19.0. In 1963, the national rate was 18.5 per 1,000; at Mercy Hospital 16.2.

Obstetricians cannot take credit for all of this improvement. The great contributions by research personnel, the improvements in anesthesia, the development of sulfa drugs and antibiotics, the universal availability of blood and the great efforts by pediatricians have all combined to help. However, much of the credit must go to obstetricians. The improvement in training, both in the specialty of obstetrics and in improved facilities for training general practitioners; the increase in numbers of deliveries in hospital, and the great increase in scope of prenatal care, have all been major factors. Obstetrics has changed from midwifery or, as it once was, a subspecialty of surgery, into an honored and respected specialty in its own right.

That we still have problems, all must admit. It may be valuable to review some of these briefly.

Chairman's Address: Presented before the Section on Obstetrics and Gynecology at the 94th Annual Session of the California Medical Association, 28 to 31 March 1965.

It may come as a surprise to realize that some of our most important problems are still the same old ones we have had all along. In the splurge of writings about some of the newer and more glamorous conditions and procedures, these old enemies may be overlooked, even though they are the frequent, common and more important. In obstetrics, as in all medicine, the new and exciting things take first attention, but then fade as time and thought gives a more accurate assay of importance, and sink back to their rightful smaller place. The old seem ever with us.

Abortion remains one such enigma, for after all the suggested ritualistic procedures, gallons of orange juice, pounds of progesterone, administered however hopefully, we must admit that at least statistically we have made almost no progress in preventing abortion very early in pregnancy. The increased understanding of the problem with the knowledge that most abortions result from abnormal development, perhaps on a genetic basis, is helpful only in that it allows us to explain to our patients our failure to prevent its occurrence. The same holds true of prematurity. We still do not know how to prevent most premature births. So far, we cannot stop labor.

During the last 25 years the reasons for some fetal deformities have become evident. Those found following rubella are well known, and we all await anxiously the vaccine to prevent that disease, for we must admit that all other means, including gamma globulin, have been of little value. Fortunately deformities following other diseases, such as mumps and toxoplasmosis, are rare. These causes were unknown 25 years ago, just as deformities following drug administration were unknown. It is tragic that a great catastrophe such as the recent one associated with thalidomide must occur before this sort of thing comes to light. But then, all knowledge comes hard.

The cause of erythroblastosis was unknown 25 years ago. Despite discovery of RH factor, all efforts at control failed, and one could adopt an almost nihilistic attitude, until Liley came along with amniocentesis and intrauterine transfusion, which offers some hope for a few of the unfortunate. This is no ultimate answer, but it is a start.

Toxemia remains a major threat, although by virtue of the research of such men as our own Nick Assali we have made great strides, at least in controlling symptoms. The newer drugs have resulted in a decrease in serious complications, but we still have much to learn about the cause, nature and cure of the condition. Prenatal care has proved its value in prevention.

Some diseases which can still be serious when encountered during pregnancy—tuberculosis and rheumatic heart disease, for example—become relatively less important, owing to general advances in medicine. The increased number of live babies born to diabetic mothers is also an example of improved general medicine, and especially of teamwork between obstetrician and internist. This happy result could have hardly been imagined 25 years ago.

Almost all of us admit the value of prenatal care. But even this is changing. One change is a shift to group or mass education of patients, taking some of the good points from the "natural childbirth" idea, which helps patients to greater understanding and cooperation. This is a shift away from the great emotional dependence on the obstetrician which many patients developed in the past. At the moment, this seems to be good. However, time alone will place these efforts in their proper place. The great flurry over total "natural childbirth" has now so subsided that about its only vociferous advocates are a small pseudointellectual cult with almost religious fervor for it. That there are good points is not denied; these we have adopted. The great use of this procedure in Russia is often held up to us by enthusiasts, but we become somewhat disillusioned when travelers report that the best estimate is that only 60,000 women in the "institutes" devoted to this type of delivery use it, out of the more than 4,000,000 women who have babies each year.

The changes in procedures directly related to delivery are most pronounced. One of the most evident relates to medication during labor. Whereas 25 years ago women were "knocked out" by large doses of barbiturates, scopolamine, and perhaps rectal paraldehyde, we now use as little medication as we can, hoping that better instruction of the mother beforehand will make it possible to use smaller doses and result in better babies. Although there seemed to be little evidence of serious damage to newborns in older times, who can forget the sleepy babies and the odor of paraldehyde in the nursery.

Those of us who use spinal-saddle block or caudal anesthesia are convinced of its safety as compared with general anesthesia induced by gas or ether, and in the unusual event that general anesthesia must be used, we are impressed at how differently the babies react. It is dismaying, therefore, to find that in many institutions in the United States, general anesthetic agents are still the major ones used. Often this is because these hospitals, unlike most of ours in California, do not have physicians specializing in anesthesiology to administer obstetrical anesthesia.

Whereas 25 years ago there were many papers presented on the pros and cons of induction of labor, no one today denies its usefulness if judiciously employed. Even so, continuing physician education on induced labor is needed.

At Mercy Hospital in 1939 only 35.5 per cent of patients had low forceps delivery; in 1964 the proportion was 63 per cent. Midforceps delivery was used in 1.78 per cent of cases in 1939; in only 1.4 per cent in 1964. There was one high forceps delivery in 1939, none in 1964. In 1939, 2.5 per cent of births were by caesarean section; the rate was 6.7 per cent in 1964, and 50 per cent of these operations were on women who had previously had at least one extravaginal delivery, compared with only 21 per cent in 1939.

While few of us believe that caesarean section can be considered a stand-by way out of trouble, the increased rate reflects the thinking that a more liberal use of caesarean section actually is conservative obstetrics. The decrease in obvious damage to mother and baby seen after more heroic methods in times past justifies this position.

Methods of handling the third stage of labor certainly are an improvement. The knowledge that when the placenta does not readily deliver it can be safely removed by hand has often prevented loss of blood and avoided the hazards of the transfusions that otherwise would be needed. We do not advocate the routine manual removal as a clinical procedure, but we do strongly recommend exploration of the uterus after delivery of the placenta to be sure that there are no retained secundines and no lacerations which should be repaired.

Early ambulation postpartum is now universally accepted. The difference between our present procedure and the eight or nine days of bed rest that we used to think advisable is very evident. We are now less often plagued by embolism as a late sequel. My own early experience with natural childbirth and early ambulation came when I delivered a Navajo Indian woman under a tree beside a wagon during the Pow Wow at Flagstaff, Arizona, in 1936. When I went back to see how she was the next morning, the woman, the baby and the wagon had all gone on their way. This is primitive learning.

In 1939 three of a total of 1,956 women delivered at Mercy Hospital died, one from bronchopneumonia, one from puerperal sepsis of the old standard type, and one from puerperal sepsis after caesarean section that had not been done until long after rupture of membranes. In 2,887 deliveries in 1964, one woman died, of "gram-negative shock." It seems true generally that there is not only a decrease in maternal mortality but a change in type of mortality. In some series deaths have been due to non-obstetrical causes—poliomyelitis and subarachnoid hemorrhage, for example—and even those from obstetric causes are often from different types of infection, such as the septic shock variety. Mortality rates have become so low that extreme vigilance is necessary to improve them.

Eighty-three per cent of the deliveries at Mercy Hospital in 1964 were performed by specialists in obstetrics. This is a different situation from that in many hospitals. It is variously estimated that in the United States somewhere between 60 per cent and 70 per cent of pregnant women are under the care of general practitioners. Good obstetrics practiced by trained obstetricians results in good care. The efforts to improve the education of the generalist has also paid off in handsome improvements. This education is a project all obstetricians should engage in, for raising the general level of knowledge in obstetrics will provide better and better care for more and more women.

Fertility

One of the new functions thrust upon obstetricians is a part in population control. This includes studying and treating infertility. This seems a paradox in times when so many people are worried about the population explosion, but it is true everywhere that infertile women want children. With more reasonable methods of study and new agents to help with ovulation, our results improve, albeit slowly. Further success will come only with better understanding of the processes of human reproduction.

Contraception

When I was a senior in medical school at Michigan in 1932, Dr. Norman Miller presented to us behind locked doors the first lecture on contraception given to a medical school class at that institution. How far contraception has come can be realized now that there is talk of governments supplying information to whole countries. The problems attendant on world population explosion almost force mankind to do something about it. For the first time we have really effective methods of contraception, which while not foolproof, and still somewhat expensive for mass use, are simple, effective and practical. Most of us are called upon by patients for information on this subject, and I believe it is our duty, within the limits of our own religious and ethical beliefs, to supply it. I believe that many of those who speak so alarmingly about the expected growth in population and many of those who believe that most women want as many babies as possible, are in error. In light of the fact that more than four and a half million women in the United States are using oral contraceptives, the present drop in birth rate must be owing at least in part to a wish to limit family size. This field requires very careful study on the part of all of us to be sure that we do not do women damage from prolonged use of any of the new methods, tablets by mouth, intrauterine devices, or what not.

That a growing population may place great demands on obstetricians and general physicians to provide good care cannot be denied. One way that we can help in this situation is to interest promising young men in obstetrics as a profession. We should make every effort to enlist those who show interest in medicine and especially in obstetrics. Certainly no specialty offers more personal satisfaction, and we should be proud to make our position known.

We are facing threats of further inroads by paramedical personnel into fields traditionally ours. And now some of our own are suggesting further that delivery of "those not expected to have complications" be turned over to midwives. Various sorts of substitutes are suggested, from nurses given additional training, to people about half trained as physicians. I believe that these suggestions pose great danger to American women. There are many paradoxes present. At a time when great emphasis is being placed on the emotional support of pregnant and parturient women, someone suggests taking away from the women the one person on whom she depends for the greatest support, the obstetrician, and replacing him with a somewhat impersonal poorly trained interloper. American women desire private, personal care. In our local community, when the original Medicare program—when the word was used for the care of servicemen's dependents—allowed the women free choice between the available military clinic services or private physicians, 75 per cent of the women chose private care, despite the fact that the clinic care is the best that can ever be expected in mass medicine. These patients were easily absorbed by local physicians and hospital facilities. This suggests that instead of building expensive vast clinic facilities, the government might better subsidize indigent patients and use existing personnel and private hospitals for their care.

The idea of turning over for delivery "those not expected to have complications" perplexes me, for I doubt that any of us is good enough at determining which women will not develop complications at delivery—sometimes precipitously and to catastrophe. Partly trained personnel, called by whatever name, can be helpful in much of the work having to do with obstetrical practice—in prenatal clinic work, for example, or perhaps in making follow-up house calls on patients who do not show up for clinic appointments. However, to delegate to such people medical technical functions, often dependent on good medical judgment, seems to me to be a backward step. A patient's neglect of attending prenatal clinics is largely a reflection of failure of patient education, and can be corrected only by mass community efforts to convince patients that what may seem to them needless bother, is very much in the interest of their own welfare.

Patients and the community we must educate, but first and continuously ourselves. There will be changes in the tools of medicine, in our methods of practice, and perhaps even in the economics of medical care, but through them all we must never lose sight of our goal of happy, healthier mothers with healthy babies. As practicing obstetricians who understand our patients as well as we understand our goals, let us play the biggest part in determining the direction these changes take.

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Coccidioidin Retest Reaction

Observations of Tests on a Coccidioidin-Sensitive Person

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■ *The retest coccidioidin reaction in an apparently healthy person known to be coccidioidin-positive developed more quickly and was of a greater magnitude than that of an equivalent test in a virginal site in the same person. In both reactions, erythema, induration and/or edema were evident. Although the peak of the retest reaction was at 12 hours, readings made at 24 and 48 hours were in a definitively positive category.*

THE VARIATIONS in the magnitude of the local response induced by repeated intradermal injections of tuberculin skin test antigen in exactly the same injection site in humans known to be sensitive to tuberculin have been described. However, the presence or absence of a parallel phenomenon, identified as a "retest reaction,"[1] under similar circumstances in humans known to be sensitive to the coccidioidin skin test antigen apparently has not been explored. The "retest reaction" associated with tuberculin in humans was observed as early as 1914.[2] An extensive investigation using tuberculin in humans was also made in 1925,[4] and in the most recent investigation in 1963[1] guinea pigs were used. In his investigations in 1914 Koch used the scratch technique of testing. In 1925 Weiss[4] reported mainly on the results of scratch testing with tuberculin, but stated that similar results in retesting were also obtained with intradermal testing. The general result of tuberculin retesting in positive-reacting individuals was an acceleration of the development and increases in size of the reaction so that the peak was reached before 24 or 48 hours.

The purpose of the present communication is to report the skin test results obtained in virginal and retest areas in a coccidioidin-positive person who was apparently in good health.

Methods

An apparently healthy white man, aged 37, who was known to be coccidioidin-positive,[3] was the subject for this illustrated investigation. The previous history of this person included testing with a standard 1:100 dilution of coccidioidin* on 22 August 1960, which produced erythema and edema 35 by 45 mm and induration 16 by 17 mm at 48 hours. A dilution of 1:1000 coccidioidin given on 13 February 1961 produced mild erythema and induration which measured 8 by 7 mm.

For the present investigation the retest site on the front forearm was conditioned, beginning 4 August 1964, by giving five consecutive weekly skin tests in exactly the same place. One tenth ml of commercial coccidioidin (standard 1:100 dilution) was used for all except the first test, for which a 1:1000 dilution was used. Skin tests were given with disposable needles and syringes. Readings were made at 15 minutes and at 6, 12, 24, 48,

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and 72 hours. Areas of erythema, induration and edema were measured. At the sixth week two skin tests were given, one in the retest area and one in a virginal area 6 cm from the retest site, and toward the hand. Readings were made at the same time periods mentioned above. Photographs were taken at 30 minutes and at the later intervals listed above with the exception of 12 hours. Two views, top and lateral, were taken at each time period.

Results

The first skin test of the present series using the 1:1000 dilution of coccidioidin was negative. All subsequent skin tests with 1:100 dilution coccidioidin were positive.

At the sixth week the 15-minute response at the retest site was manifested as an area of induration and erythema 11 by 12 mm; in contrast the virginal skin test response was negative. At 30 minutes two small, papular, hive-like lesions were observed on the periphery of the erythematous zone at the retest site; these were relatively transient, appearing abruptly and subsiding rapidly. Similar lesions were noted on two occasions during the conditioning period of weekly retests. The time intervals at which they developed were not consistent, and in all instances they had completely disappeared within an hour.

The retest reaction continued to enlarge, and at six hours the area of induration and erythema was 12 by 15 mm (Figure 1). Comparative erythema and induration at the virginal site measured 5 by 6 mm. During the ensuing six hours, the reaction at the retest site progressively expanded and at 12 hours erythema measured 25 by 30 mm and induration 15 by 15 mm. A similar increase of the magnitude of reaction, although to a lesser degree, occurred at the virginal site during the same period; at the twelfth hour both induration and erythema measured 11 by 12 mm.

At 24 hours the intensity of the reaction in the retest area had begun to subside. Induration measured 11 by 12 mm; erythema was relatively unchanged in size (30 by 37 mm) but the intensity had considerably diminished. The central area was characterized by a faint mottled pink appearance and the periphery by a concentric band, 6 mm wide, of slightly greater intensity and homogeneity of the pinkish hue. An area of frank but mild edema extended beyond the periphery of the indurated area to the limits of the erythematous reaction. In contrast, induration and erythema at the virginal site measured 16 by 20 mm.

At 48 hours (Figure 2) the dimensions of the reaction at the retest site were 8 by 7 mm for both slight induration and residual erythema of a somewhat dusky hue. The measurements at the virginal site were 8 by 9 mm of mild induration and erythema.

Only a slight residual dusky erythema and slight induration, 8 by 7 mm, in the retest site at 72 hours remained; at the virginal site, 9 by 10 mm of residual dusky erythema and mild induration persisted.

Discussion

As already described in persons who have posi-

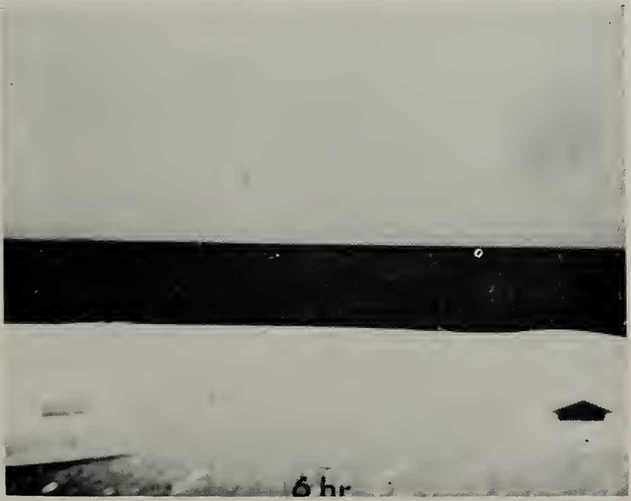

Figure 1.—Six-hour reactions of virginal (left) and retest (right) reactions using coccidioidin. At top is the view from above; below is the lateral view.

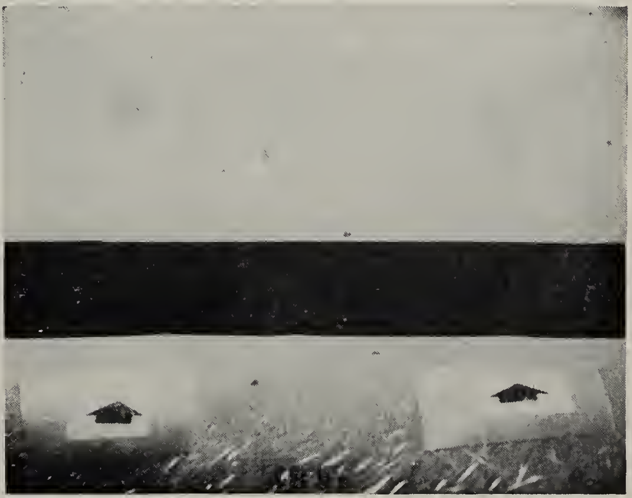

Figure 2.—Forty-eight-hour reactions of virginal (left) and retest (right) reactions using coccidioidin. At top is the view from above; below is the view from the side.

tive reaction to tuberculin in the retest site,[1,2,4] the coccidioidin retest reaction develops more rapidly and is of greater magnitude than is reaction to an equivalent skin test inoculation in an assumedly virginal area in the single subject tested. The peak intensity of reaction at the retest site appeared to be attained some 12 hours before an equivalent peak response in a virginal site. Nevertheless, the accepted 48-hour observation for definitive categorization of positive or negative was not compromised, because the measurements were essentially equal at both the retest and virginal sites. It is thus assumed that in the majority of the apparently healthy population there would be little difficulty in the assessing of the coccidioidin skin test reaction if the skin test were inadvertently given in approximately the same site as a preceding and relatively recent positive reaction. What the retest response and its significance would be in clinical cases of coccidioidomycosis is not known, nor does it seem appropriate to derive implied conclusions relative to clinical coccidioidomycosis from the results obtained in the single, very limited investigation.

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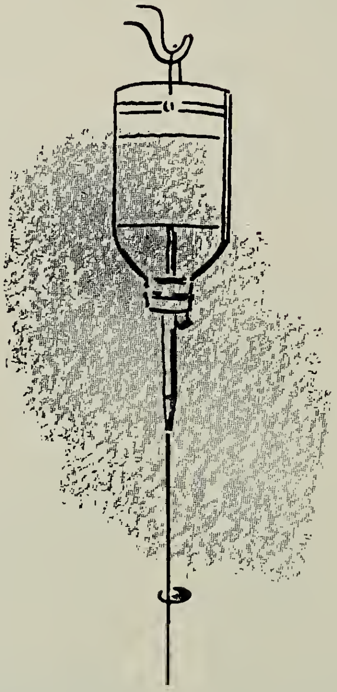

Renal Homotransplantation

Current Status

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■ *Five years of clinical experience with renal transplantation has led to improved results in terms of surgical technique and the use of immune suppressive drugs.*

The duration of function of individual grafts is entirely uncertain at present. Some prognosis can be based upon the source of the graft.

There is evidence to suggest all grafts will be destroyed by host factors.

The employment of tissue-matching techniques offers the most promise for improved results in the immediate future.

AT THE UNIVERSITY OF CALIFORNIA, Los Angeles, Health Center we have had five years' clinical experience with drugs to suppress the immunologic rejection of renal homografts. The combination of azathioprine (Imuran), Actinomycin C (Sanamycin) and prednisone has been the most effective. Other agents were tried before azathioprine was available.[5] Although the results of clinical experience are far from satisfactory, it is notable that prolonged function of some grafts has been achieved. Long-term survivors with renal grafts are not the immunologic cripples one might anticipate. Although many patients die shortly after operation from infections with bacteria, yeast and protozoa-like organisms, many pass through the critical postoperative period and go on to lead nearly normal lives.[6,23] The remarkable rehabilitation of these patients with renal grafts is incentive to the surgeon to continue clinical investigation.

Selection of Recipients

Clinical renal transplantation, exception in the case of twins, remains an experimental procedure, as the outcome of the individual case is not predictable. Only patients with irreversible terminal renal failures are candidates to receive a graft. A systemic disease such as lupus erythematosus, diabetes mellitus, or generalized vasculitis in the recipient, is a contraindication to a graft from a living donor. A cadaver kidney might be considered in these cases. The presence of uncorrectable lower urinary tract disease, which might predispose to urinary tract infections, is considered a contraindication. In the UCLA series recipients whose primary disease was glomerulonephritis have done much better than those with pyelonephritis. We relate this to the presence of infection in the urinary tract of the recipient, which is a serious problem in the patient about to receive immunosuppressive therapy. Infection accounts for a large number of the early failures.

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Preparation of Recipients

As a result of increased knowledge and skill with dialysis, we find patients now come to surgery in remarkably good condition. Most recipients have undergone numerous dialysis procedures over a period of weeks or months. This may be necessary in most cases but may not be desirable. The numerous blood transfusions administered in this program may jeopardize the graft by previous exposure to antigens. The transfused lymphocytes could carry antigens shared by the graft which would sensitize the recipient. In several cases in the UCLA series, a violent rejection crisis occurred three to four days following transplantation. A "second set" reaction seemed probable. Most of these rejection crises have been reversed by intensive immune suppressive therapy. The role of this form of early rejection in the long-term survival of the recipient has not been determined.

Recipients whose primary disease is pyelonephritis and in whom active urinary tract infection is present are best treated by preliminary nephrectomy with an intensive effort to eradicate all infection from the remaining urinary tract. Eliminating infection from the urinary tract is difficult in patients with little or no renal function. A prospective recipient with severe hypertension was similarly treated with preliminary bilateral nephrectomy, following which the hypertension was more amenable to medical management.

Selection of Donors

Sufficient clinical experience with renal homotransplantation throughout the world is available to allow some prognostication based upon the source of the kidney graft. Table 1 relates the survivors of renal transplants to their donors for grafts performed in a 12-month period, 16 March 1963 to 15 March 1964, as reported to the Renal Transplant Registry.[17] A 12-month follow-up was available on 15 March 1965 so that the patients listed "alive" represent survival of one year or longer. The advantage of having a donor who is a close blood relative waiting in an adjacent operating room is clear. Even with this favorable arrangement the random use of a blood relative allows only approximately 50 per cent survival to one year or longer. The result of attempts to provide a scientific basis for donor selection will be discussed later in the paper.

TABLE 1.—*Results of Kidney Homotransplantation 16 March 1963 to 15 March 1964*

Donor	*Number of Transplants*	*Number Alive*	*Per Cent Alive*
Parent	79	35	44
Sibling	46	29	63
Unrelated	23	4	17
Cadaver	63	10	16

For many deserving patients who do not have a suitable living donor a cadaver kidney is the only alternative. Although this source of organs has the advantage of mitigating the moral problems associated with renal transplantation from living donors, it adds considerably to the technical problems of achieving a functioning graft. The number of organs available from cadavers is limited. The best sources have been patients who die of intracranial hemorrhage or brain tumors and during or after cardiac operations. Despite very discouraging results initially, there has been some improvement in the outcome with cadaver organs. The importance of early, rapid cooling of the graft is clear. This is best accomplished by intra-arterial infusion with a cold salt solution. We have obtained good results with lactated Ringer's solution previously stored in a refrigerator at approximately 4 degrees C. Other investigators add procaine, heparin and colloid to the perfusate.

A kidney removed from a patient who died following a cardiac operation was recently used at UCLA Health Center. The heart was massaged and 100 per cent oxygen was supplied by respirator for more than two hours before nephrectomy. Immediately after removal, the kidney was cooled by an infusion of 500 ml of cold lactated Ringer's solution. Although three more hours elapsed before revascularization, the transplanted kidney functioned immediately and 14 liters of urine was excreted in the first 24 hours after operation. Over the ensuing week the patient's serum creatinine fell to normal.

Technique

The iliac fossa offers the most favorable location for the surgical procedure. The internal iliac artery can be employed for end-to-end anastomosis with the renal artery, as these vessels are of similar caliber. Ureterocystostomy is the simplest method of dealing with the transplanted ureter and we feel it is the best procedure because of its simplicity. We have found that the site at which technical complications most frequently occur is the point of anastomosis of the ureter to the bladder. Although a temporary urinary fistula may be well tolerated in patients not being treated to suppress immune reaction, it can frequently cause death in the recipients of renal graft. Long standing uremia, poor nutrition and the catabolic effects of antimetabolites and corticosteroids all play a role in the serious consequences of urinary fistulas. Despite these handicaps a fistula will heal in some patients, who then may go on to long-term survival. When the kidney is obtained from a living donor bilateral nephrectomy in the recipient is usually performed at the time of renal grafting. It has been delayed or not performed at all in patients receiving cadaver grafts because the outcome is considerably more in doubt.

Splenectomy has always been controversial. It has no proven value to the survival of the graft, and reports of increased susceptibility to infection and thromboembolic phenomena are accumulating.[8]

Thymectomy in the newborn mouse produces a profound alteration of the immunologic system but is of no proven value in man.[32] Our present concept holds the thymocyte to be disseminated throughout the body in the adult (lymph nodes, marrow), so that removal of the thymus in the adult would not remove the potential of this system.[3]

Biological and statistical proof may be lacking but the early experience with thymectomy in renal grafting at Denver was favorable, suggesting that more evaluation is indicated.

Immune Suppression

The basic drug in suppression of immune reaction is the antimetabolite azathioprine (Imuran®). This is an imidazolyl thiopurine which is thought to inhibit lymphocyte replication by interfering with nucleic acid synthesis. The desired suppression of the immune response is obtained without a depression of the total number of leukocytes or of lymphocytes in the peripheral blood.

Azathioprine is often started one or two days before operation and then given somewhat empirically in a dose of 1 to 3 mg per kg of body weight daily for an indefinite period. Canine renal grafts have been observed to survive with good function when azathioprine (or 6-mercaptopurine) was withdrawn many months after transplantation.[21,33] A similar experience has not yet occurred in human renal transplantation.

The leukocyte count is used to measure toxicity to azathioprine. Leukopenia is not a desirable sequela of this therapy as satisfactory immune suppression is achieved without a depression of leukocytes in peripheral blood. Patients with decidedly impaired renal function do not tolerate the dose of azathioprine used in persons with good function. This becomes a problem in recipients of cadaver organs in whom a 10-day interval of anuria may occur. Our plan is to give small daily doses (0.25 to 0.5 mg per kg of body weight during anuria) whenever the leukocyte count is adequate. We have observed evidence of rejection when azathioprine was withheld even during severe leukopenia.

In many centers, prednisone is started at the time of operation in a dose of 30 to 60 mg per day. This may be increased to 100 to 300 mg per day at the time of rejection crisis.

Almost all recipients exhibit an initial acute rejection crisis in which diminished renal function is the cardinal manifestation. This may follow a progressive course for two to five days, after which renal function almost invariably returns to the precrisis level. When renal function is again maximum, the dose of prednisone will be reduced to approximately 60 mg per day. This dose is in turn gradually decreased until it reaches a maintenance level of 15 to 30 mg daily, approximately three months after operation.

Actinomycin C, an antibiotic which is cytostatic by its inhibition of transfer ribonucleic acid, is used at the time of rejection crisis in daily doses of 200 to 400 mcg. This drug is not generally employed for a long term, but as adjuvant therapy.

Local irradiation of the transplanted kidney has been observed to be beneficial when used immediately after operation.[9,11] In the animal laboratory we observed no effect from irradiation during a rejection crisis and are doubtful of its effect clinically in this stage. We have used local irradiation (150 r) to the graft on the day of operation and on alternate days for three to four doses. This was the best schedule in experimental renal grafts in dogs. Such irradiation has a questionable effect upon the basic immunologic reactions involved, but it may play a role as an anti-inflammatory agent.

Several other methods of immune suppression are being tested in the laboratory and on a limited scale clinically. Thoracic duct fistula which removes a large number of lymphocytes in addition to protein and lipids has a profound effect upon the immunologic reaction of the patient.[18,24,27]

This procedure is being tested in a few centers. Considerable technical difficulty is inherent in maintaining the fistula, and pronounced nutritional impairment occurs if the protein and lipids are not returned or replaced. Thoracic duct fistula may be more useful as a tool in the investigation of immunologic mechanisms than as a clinical procedure for immune suppression in patients.

Heterologous antilymphocytic sera, which will induce a significant lymphopenia in laboratory animals, can be produced.[16] The application of this technique to humans carries all the problems associated with the use of heterologous serum. Homologous antilymphocytic sera can be obtained but the potency of these sera is not established.

Destruction of lymphocytes by the technique of extracorporeal irradiation is possible.[2,26] The effect of this means on the immunologic response has not yet been tested sufficiently in the laboratory to indicate its effect in man. The procedure involves the maintenance of a chronic arteriovenous fistula similar to that used in chronic hemodialysis. This is a difficult technique in the animal laboratory but could be relatively easily accomplished in humans. Since many patients come to transplantation with an arteriovenous shunt already constructed for previous dialyses, it is practicable in man.

Pretreatment of the recipient with antigen is very effective in rodents but of questionable value in larger experimental animals and man. Present efforts are focused on obtaining concentrated antigen from subcellular fractions.[31] The long range goal of this form of investigation is intriguing. The aim is to produce a specific tolerance to the graft in the recipient and not affect other immunologic reactions. This may be looked upon as the long-range goal in the investigation of the graft rejection process.

Prognosis

As indicated earlier a compilation of the experience of all transplantation centers throughout the world gives us a rough guide as to what to expect from individual efforts. As technical skill with the operative procedure and the management of new suppressive drugs progresses, past results are improved upon. The results from individual centers vary somewhat according to the area of primary interest and the total experience achieved. Starzl and coworkers in Denver have achieved remarkable results with living donors, particularly close blood relatives.[25] Investigators in Cleveland[19] and Montreal[10] have focused their principal effort on transplant of cadaver kidneys with remarkable results. At UCLA we have used both living donor and cadaver kidneys with increased numbers of patients going on to long-term survival, as a result of lessons learned with previous cases.[4,12]

New Diseases

With the success of efforts to prolong the life of patients who are terminally ill with chronic renal failure, it has become apparent that we are allowing these patients to survive and become afflicted with new diseases. Transplantation of cadaver kidneys removed from donors who had had carcinoma resulted in the transplantation of malignant disease in two patients.[14,20] Histoplasmosis has been transmitted in a similar manner.[10] Although the availability of cadaver organs is limited, one must always keep in mind the possibility of a transmission of disease and attempt to avoid this unfortunate sequela.

One of the remarkable observations in the case of a patient who had chronic uremia with anemia was the spontaneous improvement in hematocrit and red blood count following successful renal transplantation. A case of an excessive hematopoietic response with erythremia has been reported.[20]

It has long been recognized that patients with chronic renal failure have secondary hyperparathyroidism as the endocrine system attempts to correct the electrolyte imbalance. Persistence of this hyperparathyroidism by the apparent autonomous overfunction of the parathyroid glands has been reported in the recipient of a renal homograft who achieved good renal function. Surgical therapy was necessary to correct this antonomous secondary hyperparathyroidism.[15]

A disturbed immunologic system in the recipients of renal grafts is evidenced by the reports of arthritis and neuropathic conditions.[29] We have seen an example of each of these. A 20-year-old girl who has survived with a renal graft from her mother for two years was observed to have definite synovial thickening and fluid in both knees. These signs appeared more than a year after the transplantation. A 46-year-old man who received a cadaver kidney from a donor with brain tumor had minimal peripheral neurologic deficit involving his feet at the time of transplantation a year ago. Two and a half months after renal transplantation he had a rapidly progressive neuropathic condition which ultimately extended to the mid-abdomen, involved the upper limbs and began to involve the circumoral area, nose and tongue. The empirical administration of increased amounts of prednisone was followed by a very slow recession of this neuropathic state. The patient is currently ambulatory with a residual neurologic deficit in excess of that found at the time of transplantation. Since the neuropathic condition in this patient developed and progressed a considerable time after he had excellent renal function, it is unlikely that it was of uremic origin.

No doubt in the future there will be increased numbers of cases reported with findings similar to those above and with new disease processes which are a consequence of the prolongation of life and the methods necessary to achieve it.

Histocompatibility

When technical factors are equivalent, the observed fate of an individual renal graft is likely determined by the degree of histocompatibility between donor and recipient. The identification of these factors is the goal of those involved in "tissue matching." Both Walford and Terasaki of UCLA use the antigens of the lymphocyte to represent the antigens of the graft. Antibodies which kill the lymphocytes serve to identify the presence of antigen—a lymphocyte cytotoxic test. The antigens of donor and recipient are identified as similar or dissimilar from the reaction of lymphocytes with a panel of antibodies.

Terasaki has made a retrospective study of many successful renal grafts and found the "match" was favorable in patients who had prolonged function.[28] A prospective study with living donors, both related and unrelated, is currently in progress in Denver.

Walford is making skin grafts between human volunteers to relate graft survival to the "match."[30] Preliminary observations from work with the lymphocyte cytotoxic antibody matching test appear to be most encouraging.

Other methods to test histocompatibility have been described. Brent and Medawar demonstrated that a simple intradermal injection of lymphocytes can be employed as a histocompatibility test in guinea pigs.[1] The clinical application of this test has not been as successful or as easy in humans.

Hirschhorn found that the lymphocytes from individuals with decidedly dissimilar antigenic make-up, proliferate in an accelerated manner in vitro.[7] This reaction suggests a method to identify antigenic similarity or differences based upon the rate of proliferation of cells in vitro.

Observations on Long-Term Survivors

Patients who pass through the first few months after operation and go on to long-term survival with good renal function can live nearly normal lives. They are monitored as to leukocyte count and renal function at intervals of one or two weeks. The manifestations of homograft rejection reaction in such patients are very subtle when compared with the initial acute crises. In our experience the only manifestation that we have found dependable is a deterioration in renal function with an elevated serum creatinine and blood urea nitrogen. Treatment at this time is again the administration of increased doses of prednisone with Actinomycin C and occasionally local irradiation to the graft.

Persistence of mild to moderate hypertension has been observed in seven of thirteen long-term survivors in the UCLA series.

The examination of renal biopsy specimens from long-term survivors who are clinically well with excellent renal function by standard methods of determination, reveals disturbing findings. With rare exception, the kidneys have undergone pronounced vascular changes characterized by intimal thickening of the intrarenal vessels. These vascular changes are independent of hypertension in the host.[22] If these lesions are progressive, the ultimate destruction of the graft is certain.

Many investigators feel that all homografts will be ultimately destroyed by the immunologic system of the host and that histocompatibility factors will decide the duration of function. A system of precise tissue "matching" could alter this prognosis.

Future Goals

The transplantation of organs from living donors will always represent a moral issue to those concerned. Since satisfactory function can be achieved with the cadaver kidney, this source holds great hope for the future.

We feel that the application of tissue matching tests could greatly improve the prognosis with the cadaver kidney and nullify the disadvantage of a graft from an unrelated person with different genetic and antigenic make-up. Since cadaver organs are at a premium, we plan to have a number of potential recipients matched and waiting for a suitable graft. When a transplantable kidney becomes available, the tissue match would be made and the best recipient or recipients selected from a large panel of potentials. Such a program would undoubtedly require a number of recipients, perhaps 20 to 40 as our experience with the matching of volunteers for skin graft suggested this number. Chronic dialysis will play an important role in the maintenance of patients waiting a cadaver graft.

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CASE REPORTS

Use of a Serosal Patch in Repair of a Duodenal Fistula

Clinical Application of an Experimental Method

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REPORTS BY Jones,[1,2] Kobold,[3] and Wolfman[4] have recently appeared in the literature describing an experimental method of closing acute or chronic duodenal fistulas in dogs by covering the defect with an unopened loop of jejunum, making in effect a "serosal patch." No clinical cases utilizing this technique were reported by them. We recently applied this method in treating a patient for whom no other solution appeared to give any hope of success.

Report of a Case

A 54-year-old man, an alcoholic, was admitted to hospital 6 September 1964 because of hematemesis and melena. Initial laboratory reports were as follows: Hemoglobin 9.5 gm per 100 ml prothrombin time 85 per cent of normal, total protein 5.3 gm per 100 ml with 3 gm albumin, total bilirubin 1.84 mg and blood ammonia 51 mcg per 100 ml.

The patient remained in satisfactory condition until September 9, when massive bleeding began. A Blakemore-Sengstaken tube was passed and pituitrin was given intravenously, but bleeding continued. That afternoon an emergency end-to-side portacaval shunt through a long subcostal incision was carried out with extreme difficulty because of an immense abdomen. After completion of the shunt the patient's general condition was satisfactory, so a decision (in retrospect, unwise) was made to do pyloroplasty and vagotomy to decrease the risk of post-shunt ulcer. A standard Heineke-Mikulicz pyloroplasty was done with a one-layer closure of 4-0 silk. Vagotomy was attempted, but because of technical difficulties it could not be completed. Cholecystectomy and liver biopsy had been done before completion of the shunt. The patient required 21 pints of blood before and during operation. Except for a brief period of somnolence on the second postoperative day when the blood ammonia was 260 mcg per 100 ml, he did well until September 13, when Staphylococcus aureus was cultured from the middle of the incision around the Penrose drain. On September 14 the lateral aspect of the infected wound was opened. The following day gastric juice was found to be draining around the omentum which could be seen at the level of the skin about the drain site.

As the general condition of the patient appeared unchanged, repair of the fistula was delayed until September 17 while antibiotics and general supportive care were given. On September14, serum bilirubin was 3.96 mg per 100 ml. On September 16 total protein was 4.8 gm per 100 ml, with albumin 2.44 gm. With a nasogastric tube in place very little fluid drained from the fistula, but in the two days before closure of the fistula, gastric aspirate totaled nearly 7,000 ml.

On September 16, eight days after the first operation, closure of the pyloric fistula by the "serosal patch" technique was carried out (Figures 1 and 2). The infected, eviscerated wound was reopened, and the first loop of small bowel that presented itself (probably distal jejunum) was brought over the colon and sutured over the pyloric defect serosa-to-serosa with interrupted sutures of 4-0 Tevdek.® The defect, approximately 3 by 1.5 cm, resulted from partial dehiscence of the pyloro-

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plasty. This communicated with a small subhepatic collection of fluid. After the "serosal patch" was completed, the jejunal loop was found to take such an abrupt turn in the depths of the subhepatic space that obstruction at this point seemed very likely. Therefore, a by-pass entero-enterostomy was done as a safeguard. Through a gastrostomy opening a No. 18 French catheter with many side holes was inserted into the stomach for aspiration, and a No. 14 French catheter was threaded past the pyloric defect into the third portion of the duodenum for suction and later feeding. A sump drain was inserted into the subhepatic space through a separate stab wound to insure adequate drainage.

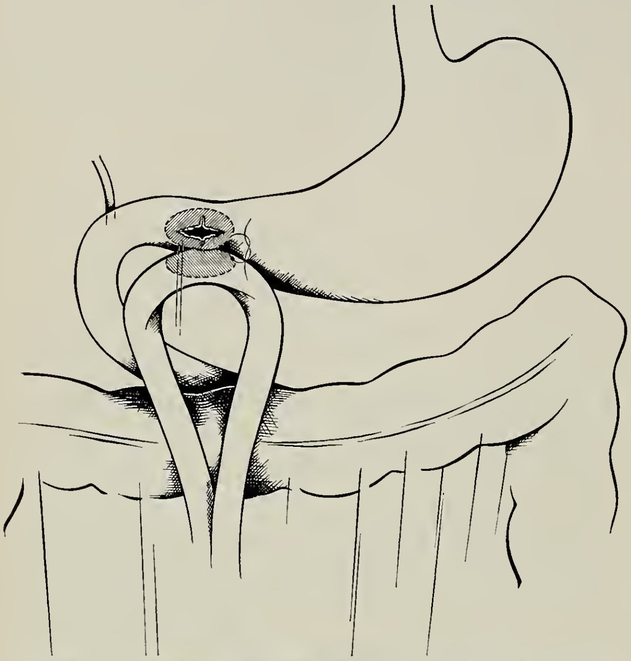

Figure 1.—Diagrammatic representation of an unopened jejunal loop being sutured serosa-to-serosa to close the pyloric fistula resulting from a Heineke-Mikulicz pyloroplasty.

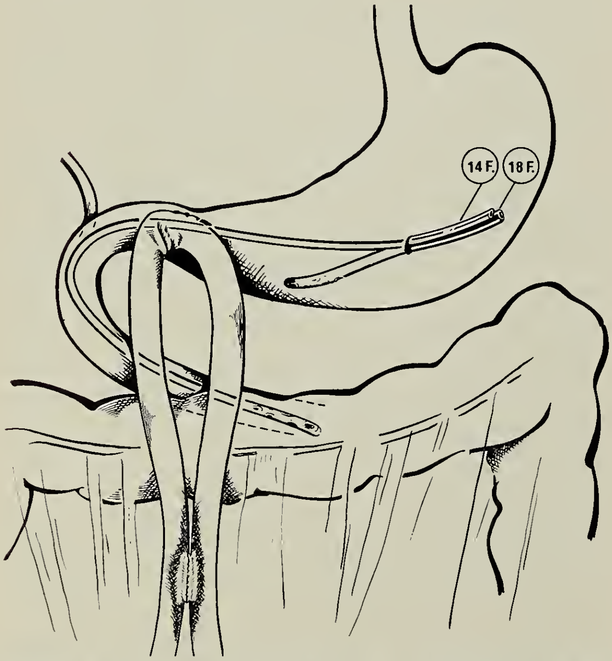

Figure 2.—Operation complete with the pyloric fistula plugged by the "serosal patch." A No. 18 French catheter was used for aspiration of the stomach and a No. 14 French catheter was threaded into the distal duodenum for feeding. A sump drainage tube (not depicted here) was placed near the "patch" in the subhepatic space. An entero-enterostomy was done to prevent obstruction of the loop.

Drainage of material from the stomach through the gastrostomy tube resumed at the previous incredible rate until the next day when propantheline (Pro-Banthine®) was given intramuscularly and magnesium aluminum hydroxide (Maalox®) was instilled into the stomach. Thereafter, gastric drainage was not unusual, and enterostomy tube feedings were begun September 20. On September 22 limited oral fluids were started, and by September 26 the patient was taking a soft bland diet in six feedings without tube supplements. Serum proteins on September 24 were still very low, with the albumin 2.1 gm per 100 ml and the total 5.1 gm.

The wound, which had been packed open from the fascia out, remained indolent. A moderate amount of serous fluid drained from around the sutures, but there was no indication of recurrence of dehiscence or of suture-line leak. On September 27 the patient was transferred to another hospital for further care. A daily low grade afternoon temperature developed but he continued to eat well and seemed to be slowly improving when he died suddenly on October 7, three weeks after closure of the fistula. A pulmonary embolus was suspected, but autopsy* showed atelectasis and toxic myocarditis as the cause of death. Bilateral subphrenic abscesses, estimated at 200 to 300 ml each, were present but no connection was found between these and the "serosal patch." The area of the pylorus was well healed without local abscess. The portacaval shunt was patent. Unfortunately, no microscopic sections were made of the "serosal patch."

Discussion

Acute and chronic lateral duodenal fistulas have always been extremely difficult surgical problems, with high morbidity and mortality rates, and little tendency to heal spontaneously. In the past, primary closure, excision with end-to-end anastomosis, gastric resection, or even pancreaticoduodenectomy have been recommended as methods of closure, but with poor results.

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*By Dr. Paul Michael, Monterey.

Jones[1] reported on a woman who required excision of a 5 cm by 7 cm portion of the wall of the descending duodenum during right colectomy for carcinoma of the colon. Successful repair was effected by retrocolic side-to-side open duodenojejunostomy. This required an open anastomosis, however, with its inherent complications.

Kobold[3] and Wolfman[4] reported a simple serosa-to-serosa closure of experimental duodenal defects in dogs by suturing an intact loop of jejunum over the hole, thereby eliminating the open anastomosis. In their experiments, the serosal surface of the jejunum was gradually covered by duodenal epithelium, the process being complete in four to seven weeks. No anastomotic leaks occurred, and there was no apparent tendency for peptic digestion of the loop.

Jones,[2] working independently, later carried these experiments even further, in that he created a duodenal defect analogous to a perforated duodenal stump, allowing the leak to continue for 20 hours. Then at a second operation the duodenal defect was closed by the "serosal patch" technique. Again, all dogs survived and no anastomotic leaks occurred. This study in infected animals is especially pertinent to the present case report.

With these excellent studies as a stimulus, the first clinical application of the method awaited only the right patient with the right problem. Certainly in the case herein reported it was inconceivable that primary closure of the duodenal defect could succeed, or that resection with end-to-end anastomosis would fare any better. The presence of infection, the poor general condition and immense size of the patient prohibited a major resection. Of course, in retrospect, the pyloroplasty should not have been done at the time of the original operation, and then no fistula would have occurred.

In spite of the Staphylococcal infection and low serum proteins, the postoperative course suggested that the "serosal patch" effectively sealed the defect. At the time of the sudden death of the patient three weeks later, he was eating a soft diet and had no evidence of recurrent fistula. Autopsy showed death due to massive atelectasis and toxic myocarditis. No evidence of anastomotic leak was found.

Additional cases will have to be accumulated and the long-term results studied, but the method gives promise of being a very simple solution to an extremely difficult problem.

Summary

The "serosal patch" technique previously used only experimentally was used in a patient who was in poor general condition and an alcoholic, to close a pyloric fistula resulting from the dehiscence of a Heineke-Mikulicz pyloroplasty done at the time of an emergency poracaval shunt for massive bleeding. Partial evisceration had occurred at the site of incision for the first operation and the wound was grossly infected with Staphylococcus aureus at the time the "serosal patch" operation was done. The patient died in another hospital three weeks later of toxic myocarditis and massive atelectasis, and at autopsy no evidence of anastomotic leak was found.

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Infectious Mononucleosis

With High Heterophile Titer and Neurological Manifestations

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THE DIAGNOSIS of infectious mononucleosis, although the disease may be strongly suspected, usually is not established clinically, until the supporting laboratory tests are secured. These consist of the characteristic "atypical" lymphocytes (virocytes, Downey cells), the elevated heterophile antibody titer for sheep cells (the pre-

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sumptive test), and the differential absorption of these heterophile antibodies by guinea pig kidney and beef heart (Davidsohn differential test). Usually, the heterophile antibody titer is considered presumptive positive at 1:112. Occasionally the titer may be elevated to a ratio of one to several thousand. The highest titer of heterophile antibodies reported in the past 10 years is 1:10,240,[3] but levels of 1:20,000 have been noted.[13] In about 15 per cent of the cases of infectious mononucleosis, titers are found to be below the significant level of 1:112.[5,14,16]

At times, unusual presenting clinical manifestations tend to confuse a definitive diagnosis. The occurrence of an extraordinarily high titer (1:229,376) of the characteristic heterophile sheep cells antibodies in the serum of a patient with severe neurological involvement prompted this report.

Report of a Case

The patient was a 16-year-old white male student who was first seen 1 September 1964 by a pediatrician* because of "sore throat" and temperature of 101°F of two days' duration. A diagnosis of acute follicular tonsillitis was made and antibiotic treatment—benzathine penicillin G (Bicillin) 600,000 U and tetracycline (Acromycin) 100 mg four times a day—and bed rest were prescribed. On 4 September, while walking about at home, the patient began to have difficulty in respiration, became cyanotic and fell to the floor with a convulsive seizure and unconsciousness which lasted approximately five minutes. He was admitted to St. Joseph Hospital by ambulance the same day. The past and family history were noncontributory. There were no previous symptoms of central nervous system disorder.

On examination no outward abnormalities were noted except for enlarged tonsils with prominent crypts filled with purulent exudate. The anterior cervical lymph nodes were moderately enlarged.

At the time of admittance, leukocytes numbered 14,700 per cu mm, of which 66 per cent were lymphocytes. Slightly more than two-thirds of the lymphocytes were atypical, having the characteristic features of Downey cells. The leukocytosis disappeared by the tenth hospital day but significant numbers of abnormal lymphocytes persisted even a month after discharge from the hospital.

The cerebrospinal fluid on the day of admission contained only 3 polymorphonuclear leukocytes per cu mm. The total protein of the fluid was 36 mg per 100 ml and the glucose content, by the oxidase technique, was slightly elevated at 76 mg per 100 ml. Blood glucose was not determined and no colloidal gold or serological tests for syphilis on the spinal fluid were done. On the fifth hospital day the spinal fluid contained 14 leukocytyes per cu mm, all of which were lymphocytes. The protein and glucose content of the fluid was 37 and 71 mg per 100 ml, respectively. Spinal fluid pressure was 160 mm of water.

Episodes of convulsions occurred daily for eight days and were described by the nurses as beginning in the right side of the face. At a later date it was noted that, when the patient was startled, the convulsive seizures began in the right leg. Gordon and Chaddock reflexes were demonstrable in the right foot at this time. With the clinical impression of possible intracranial vascular anomaly, a bilateral carotid angiogram was done on the seventh hospital day. The cerebral vascular pattern was within normal limits. The frequency and intensity of the convulsions, for which diphenylhydantoin (Dilantin®) and phenobarbital were given, diminished progressively during the period of recovery and ceased on the ninth hospital day.

The heterophile antibody titer in the patient's serum on admission was 1:229,376. On the third hospital day, it had dropped to 1:57,344 and after guinea pig kidney absorption it was still positive at a dilution of 1:28,712. No heterophile agglutinins remained in the serum following beef heart absorption.

On the sixth hospital day, leukocytes numbered 4,900 per cu mm, of which 42 per cent were normal lymphocytes, 6 per cent atypical lymphocytes, 11 per cent monocytes and 8 per cent eosinophiles. The heterophile titer was 1:28,712. The patient was discharged 13 days after admission, at which time the heterophile antibody titer had dropped to 1:4,336, the total leukocyte count was 8,200, of which 18 per cent were atypical. One month after discharge, the patient appeared in good health and free of symptoms. Heterophile antibody test was still positive to a titer of 1:448. Leukocytes numbered 9,000 per cu mm, 44 per cent of which were lymphocytes and a third of these were atypical.

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*Dr. Wendell Coffelt, whose permission to publish this case is gratefully acknowledged by the authors.

Discussion

Infectious mononucleosis is one of the few systemic diseases that is so protean in clinical manifestations that it mimics many other disease entities. In the case of mononucleosis, this apparently is due to the fact that it is a "generalized systemic disease with cellular infiltration in almost every organ, the clinical picture varying with the predominant site of involvement."[14] For this reason, many of the unusual presenting signs and symptoms are erroneously classified as "complications" although they are in fact different facets of the same disease. The reported incidence of central nervous system involvement in patients with infectious mononucleosis has varied between 1 per cent[1,4,12] and 9 per cent.[6,7] It is said to be more common in males than females, in adults than in children and rare in Negroes. The neurological symptoms usually appear between one and three weeks after the onset of the disease, but occasionally earlier. Many different types of involvement have been reported, most commonly meningoencephalitis, often associated with Guillain-Barré syndrome. Peripheral neuropathy and optic neuritis are less frequent.

The pathogenesis of the central nervous system involvement has not been established but the cause is thought to be direct viral invasion of the brain. The spinal fluid findings are variable.[2] There may be no change, or an increase in total protein and leukocytes, sometimes accompanied by an increase in pressure and an abnormal colloidal gold curve with a midzone rise. The glucose, chloride and serological tests for syphilis are usually normal. The overall mortality rate of infectious mononucleosis is less than 1 per cent, while that of patients with central nervous system complications has been reported at 11 per cent by Nichols and Athreya[11] and as much as 40 per cent by Lawrence.[8] The most common cause of death in patients with central nervous system involvement is respiratory paralysis. Few reports of postmortem studies are available. In a study of 30 cases, Lukes and Cox[10] described foci of myelin degeneration and round cell infiltrates, particularly in the leptomeninges and nerve roots. Erwin[4] also noted such phenomena.

The clinical symptoms, the classical positive serological tests and changes in the peripheral blood established the presence of infectious mononucleosis in the patient reported here. The percutaneous carotid angiograms fairly well excluded the presence of other organic disease in the central nervous system. The onset and resolution of neurological symptoms paralleled the onset and clinical recovery from the infection. This, plus the slight spinal fluid pleocytosis, help establish the relationship between the central nervous system involvement and the infectious mononucleosis.

The most striking finding in this patient was the extremely high heterophile antibody titer—1:229,376, which was doubly checked. It was not until the third day of illness, when the titer had decreased moderately, that the Davidsohn differential test was performed and the type of antibody was found to be characteristic. Similarly high heterophile antibody titers have not been noted in reports of other cases of central nervous system complications. On the contrary, in most such cases the titers were in the low normal, equivocal or slightly elevated range. It would appear, therefore, that there is no direct correlation between the heterophile titer and the severity of the clinical symptoms or the neurological involvement. It is recognized that the heterophile antibody test, first described by Paul and Bunnell in 1932 and later modified by Straus,[16] is a nonspecific or presumptive test for the disease entity. Note is taken of the fact that approximately 15 per cent of the patients with infectious mononucleosis do not have significant heterophile titers.[3,5,16] The unusual response in such cases may be explained by antigenic variability of the infectious agent or by anergy of the patient, phenomena about which more may come to light in the currently emerging concepts of immunogenetics.[17] Some investigators report a very much lower incidence of heterophile-negative patients with infectious mononucleosis,[3,9] but this is due to their acceptance of a lower limit (1:64) as evidence of a positive test. Since a relatively high proportion of normal controls have titers up to 1:112,[15,16] we consider that titer as only presumptive positive and 1:224 as positive. It is interesting to note that in the present case the titer of heterophile antibody remained elevated long after clinical recovery, whereas usually the titer declines to normal with defervescence,[16] although occasionally it may remain elevated for 30 days or more. Another interesting facet of the case here reported is that during the period of recovery the blood eosinophiles increased to 8 per cent, a fact which was considered to be of reassuring prognostic significance. Failure to demonstrate an increase of serum transaminase levels is evidence against major tissue destruction.

Summary

A 16-year-old boy with severe infectious mononucleosis with signs and symptoms of extensive central nervous system involvement and an unusually high heterophile titer (1:229,376) has been described. Other significant laboratory findings included a slightly increased spinal fluid glucose level and the persistence of an elevated heterophile antibody titer after clinical recovery.

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Esophageal Hiatal Hernia Following Vagotomy

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ESOPHAGEAL hiatal hernia may occur following vagotomy whether or not the esophageal hiatus is found to be dilated at the time of operation, although herniation is more likely if the hiatus is dilated. An asymptomatic esophageal hiatal hernia may become symptomatic following vagotomy. Surgeons should be aware of this when vagotomy is done and tighten the diaphragmatic crura if the esophageal hiatus is found to be dilated after the completion of vagotomy. Esophageal hiatal hernias should be repaired at the time vagotomy is done.

There is very little awareness of this complication following vagotomy. Kearns[1] said that diaphragmatic hernia following vagotomy is extremely rare, and that closing the peritoneum over the hiatus to prevent future herniation is not necessary. (The author is not aware that such a procedure would ever prevent an esophageal hiatal hernia.) Weisel and coworkers[2] described the hazard of associated esophageal hiatal hernia in patients having abdominal operations such as gastrectomy and cholecystectomy. They did not, however, mention vagotomy. The author has been unable to find any case reports of the occurrence of esophageal hiatal hernia after vagotomy.

The following is a report of four cases of esophageal hiatal hernia requiring operative correction following vagotomy, occurring at the Daniel Freeman and Centinela Hospitals, Inglewood, California, in the past 10 years.

Reports of Cases

CASE 1. A 48-year-old white woman had bilateral vagotomy and subtotal gastrectomy on 3 May 1956 for a chronic intractable duodenal ul-

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Submitted 8 July 1965.

cer. The space between the diaphragmatic crura and the esophagus admitted three fingers. Postoperatively, she had a partial efferent loop obstruction which persisted for about 14 days. This may have contributed to the following symptoms. Beginning in October 1957, she began to have heartburn, belching and regurgitation of food at night, unrelated to the type of food eaten. Dyspnea, cough, palpitation and tachycardia occurred during the regurgitation of food. An upper gastrointestinal series on 15 January 1957 showed a moderate-sized esophageal hiatal hernia. Intensive ulcer management for one month did not bring about improvement.

On 22 February 1957 transthoracic esophageal hiatal herniorrhaphy was performed. Five sutures of No. 2 silk were required to close the defect.

Upper gastrointestinal series of 25 April 1957 and 8 March 1958 showed no evidence of recurrence. The patient remained asymptomatic thereafter.

CASE 2. A 28-year-old white man had a bilateral vagotomy and subtotal gastrectomy on 14 June 1960 for chronic intractable duodenal ulcer. The esophageal hiatus was not dilated at the time of vagotomy. The postoperative course was uncomplicated, but about three weeks after operation he began to have belching and regurgitation of bile three to four hours after eating. The symptoms gradually became so persistent that the patient became afraid to eat. During the next four and a half years, medical treatment with antacids, antispasmodics, tranquilizers, Urecholine® and Acidulin® did not give this patient any lasting relief. Repeated upper gastrointestinal series, electrocardiograms, x-ray films of the chest and a barium enema study failed to explain this patient's symptoms. An esophageal hiatal hernia was not found. A gastric analysis on 11 November 1963 did not show free hydrochloric acid.

On 4 January 1965 without a definite preoperative diagnosis, the abdomen was opened at the site of the previous upper midline scar. A moderately large esophageal hiatal hernia, which admitted the entire hand between the diaphragmatic crura and the esophagus, was observed.

The crura were closed snugly behind the esophagus with No. 2 silk, using the Allison technique. The gastric fundus was also sutured to the undersurface of the diaphragm. The symptoms were completely relieved.

CASE 3. A 61-year-old white man had bilateral vagotomy and subtotal gastrectomy done on 18 May 1955 because of a chronic duodenal ulcer with recurrent hemorrhage and obstruction. The esophageal hiatus admitted two fingers between the diaphragmatic crura and the esophagus, and was considered to be slightly dilated.

On 5 May 1956 the patient said that his stomach had been filling up rapidly during eating for the past three weeks. He also had bloating and moderately severe epigastric pain after meals, with dyspnea on lying down. An upper gastrointestinal series on 6 April 1956 showed a well functioning gastro-enterostomy and a large esophageal hiatal hernia. Two gallbladder x-ray series were performed and the gallbladder was not visualized. Intensive medical treatment failed to relieve this patient's symptoms, and on 7 December 1957 a large incarcerated esophageal hiatal hernia was repaired transabdominally by the Allison technique. The gallbladder was thickened and without stones. This patient remained free of the preoperative symptoms up to the time he died, 31 May 1961, of coronary occlusion.

CASE 4. A 44-year-old white man had a history of a severe chronic bronchial asthma. On 10 May 1956 bilateral vagotomy and posterior gastrojejunostomy were performed for a chronic intractable penetrating duodenal ulcer with repeated hemorrhage (melena). The esophageal hiatal ring at the time of vagotomy admitted two fingers between the crura and the esophagus. Before this operation the patient had complained of regurgitation of food and heartburn.

On 1 November 1957 the patient was examined because of increasingly severe epigastric pain and burning going into the lower substernal area, occurring mainly after supper, and partially relieved by antacids. On 15 November 1957 an upper gastrointestinal series showed a well functioning gastro-jejunostomy, a scarred duodenal bulb without evidence of an ulcer crater and a large para-esophageal diaphragmatic hernia.

On 2 December 1957, transabdominal repair was done. The patient continued to have severe asthmatic attacks which were thought to complicate the operative results. Intensive "ulcer therapy" was carried out between operations, with little or no relief of symptoms. He began to have regurgitation of food on lying down and heartburn on bending forward. A recurrence of the para-esophageal hiatal hernia was demonstrated by x-ray examination on 5 March 1958.

On 20 November 1958 transthoracic repair of a large incarcerated esophageal hiatal hernia was performed, and the site of repair was reinforced with nylon mesh. The lower esophagus was now found to be shortened and chronically inflamed.

In January 1960 the patient had influenza for five weeks and vomited daily. This was followed by recurrence of epigastric pain and regurgitation of food. An upper gastrointestinal series on 7 March 1959 and again in May 1961 showed a small para-esophageal hiatal hernia with regurgitation of barium into the esophagus. The patient received constant medical management for ulcer, with gradual worsening of the above symptoms, and in addition nausea, vomiting, dysphagia, regurgitation and extreme epigastric tenderness.

On 26 October 1963 a para-esophageal hiatal hernia with one fourth of the stomach lying incarcerated above the diaphragm was demonstrated in an upper gastrointestinal series.

On 3 December 1963 subtotal gastrectomy and repair of the recurrent esophageal hiatal hernia was done. A search was made for incompletely divided vagus nerves, but none were found. The gastrectomy was done in an effort to control the chronic esophagitis. In addition to repairing the esophageal crura, the gastric fundus was sutured to the abdominal side of the diaphragm.

On 18 January 1965 an upper gastrointestinal series showed no recurrence of the diaphragmatic hernia, but gastric reflux into the esophagus was demonstrated. The patient continued to have symptoms of mild chronic esophagitis in spite of constant medical ulcer management.

At each operation, an esophageal hiatal hernia was found. The roentgenologist each time had reported a para-esophageal hiatal hernia.

Comment

In three of the four cases the patients had severe disability due to the development of esophageal hiatal hernia following vagotomy and subtotal gastrectomy. In Case 1, an efferent loop obstruction may have complicated the operative result.

The fourth case was complicated by severe chronic bronchial asthma which was thought to contribute to the problem of occurrence and recurrence of esophageal hiatal hernia. (Although the roentgenologist repeatedly diagnosed this as a para-esophageal diaphragmatic hernia, at operation it was found to be an esophageal hiatal hernia).

One patient had a normal esophageal hiatal ring at the time of vagotomy. The other three had slight to moderate dilation of the ring. One of the latter (Case 4) complained of regurgitation of food before the vagotomy.

The chronic esophagitis in Case 4 was finally partially controlled by a subtotal gastrectomy in addition to the hiatal herniorrhaphy.

Conclusions

Esophageal hiatal hernia may occur following vagotomy with gastro-enterostomy or gastric resection, whether or not the esophageal hiatus is dilated at the time of vagotomy. A small asymptomatic esophageal hiatal hernia may enlarge or become symptomatic following vagotomy. In view of this, it is recommended that any dilatation in the esophageal hiatus after vagotomy be corrected and an esophageal hiatal hernia be repaired at the time vagotomy is done.

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California Medicine

EDITORIAL

White House Conference on Health

The White House Conference on Health held 3-4 November 1965 was based on ideas and not on action and its purpose, in the words of President Johnson, was "to bring together the best minds and the boldest ideas to deal with the pressing health needs of this nation." It would be well for every physician in California and the nation to consider the ideas developed and spread at the conference, a summary of which is on page 444 of this issue of California Medicine. In them can be seen a continuation of familiar threads of medicine and health that go back for many years and the appearance of new and unfamiliar threads, some of which undoubtedly will become accepted and be woven into the fabric of medical practice and community health in the future.

The tremendous fruits of medical research, the public's awareness of the basic right of man to good health and health care, the general recognition of the great potentials of scientific medicine, and the awareness of government to the health and welfare needs of the people, along with an expanding economy, are among the impelling factors leading to the present state of ferment throughout the health professions.

While the individual patient and his physician remain the key to good medical care, the health of the community and the need for community planning for health care of high quality are becoming recognized as at present the most important fields needing to be developed in the whole province of medicine and health care. The terms *community medicine* and *community planning for health care* will become increasingly familiar to physicians of the future. As viewed by many public and health authorities, the organization and distribution of medical and health care have suddenly become urgent problems. The health team seems destined to play an increasingly important role in medical care. As Harold L. Enarson, Academic Vice President of the University of New Mexico, so well pointed out, the operating-room team is well organized, the health team not so well and the community health teams are thus far not organized at all but consist chiefly of different sources of noise.

The California Medical Association through its various commissions and committees, particularly the Bureau of Research and Planning and the Committee on the Role of Medicine in Society, has taken an important step in initiating at the state medical association level mechanisms by which ideas and plans along lines just noted can be developed on a sound basis with guidance by physicians and the medical profession. These units of the CMA as well as all of its members should give much thought to the wealth of ideas expressed at the White House Conference on Health. Undoubtedly some of them must be discarded, others modified and still others improved and accepted—but all of them must be considered if the medical profession in the future is to lead the health team and is to exert leadership in the concept of and planning for community medicine and community health.

A Farewell to John Hunton

It was my privilege to know John Hunton for more than twenty-five years and to establish a close friendship with him which endured until his untimely death. Not long ago we had dinner together in Philadelphia and we spent an enjoyable evening recalling some of the interesting experiences of the past quarter century.

Jack was a warm and friendly person who covered delicate sensibilities beneath the cloak of a gay exterior. His warmth caused others to react in like manner. One had to know him well to perceive the true depth of his feelings. Loyalty to his friends was an outstanding characteristic. He possessed this quality to an unusual degree. He was honest, forthright and frank in dealing with others, but his frankness was always tempered by kindness. He was courageous and accepted the favorable and the unfavorable with uncommon equanimity. He seldom complained and tended to make a joke of misfortune.

When he came to the California Medical Association twenty-five years ago he found a chaotic, antiquated organization operating in an atmosphere of disorder. Out of this complicated and inefficient system he established order. He introduced business methods.

His efforts, at first under difficult circumstances, and his loyalty to the Association put it in a position to deal better with the serious challenges it was soon to face.

Medicine in California owes a great debt to his memory.

He was one of the early laymen to become an executive for a medical organization. He was a founder and an influential member of the organization of lay executives. It honored him on more than one occasion for his contributions to this growing profession.

His life with his beloved Pia was superbly happy. She brought to their marriage not only her fine and gracious qualities but two splendid sons. To these boys he was a combination of father and friendly older brother. They responded with an affection that was one of the great satisfactions of his life. His encouragement and gentle guidance was perhaps the influence that led them to follow the profession he loved.

As, we, his friends, honor his memory and bid him a last farewell, it is to Pia and these fine young men that our hearts go out. Their loss is great.

To Jack we say, "Fare thee well and may you rest in peace."

John W. Cline, M.D.

Automobile Injury Epidemic: The Failure of Preventive Medicine

In 1952, 57,879 cases of poliomyelitis were recorded in this country. At least 21,269 were of the paralytic type. In 1964 only 121 cases were reported, of which 94 were paralytic. The precipitous reduction in poliomyelitis cases represented the successful application of a standard epidemic control measure by preventive medicine: the prevention of development of a disease despite unavoidable exposure to the causative agent, in this case poliovirus.

By contrast more than 48,000 persons died in 1964 as a result of automobile collision injuries. Of these, more than 30,000 were occupants of vehicles. The trend has been the reverse of that for poliomyelitis—a steady uncontrolled increase. Fisher in *The Archives of Environmental Health*[1] has recently labelled the current automobile accident toll an "epidemic."

When a disease of epidemic proportions occurs, preventive medicine may attack the problem by one or more of the classic methods of control:

1. Identification and control or elimination of the causative agent.
2. Prevention of exposure to the causative agent.
3. Prevention of development of the disease even if exposure to the causative agent occurs.
4. Treatment of the disease, when contracted, to prevent or minimize its manifestations.

The reduction in poliomyelitis cases is an excellent example of epidemic control. Note, how-

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ever, that it was achieved only when it was possible to prevent development of the disease despite unavoidable exposure to the widespread virus, for elimination of the virus or prevention of exposure to it had not been possible, and treatment frequently could not prevent disability.

Analogies exist between the former poliomyelitis epidemic and the present automobile collision injury epidemic. First, it has been impossible even to identify the various causes of traffic accidents. This was corroborated recently by a leading authority[4] who said:

"The basic reasons for accidents are obscure because the causes are many and difficult in a given accident to identify. Much basic research is required on the etiology of accidents before control measures can be developed."

Second, exposure to accidents could be avoided by preventing people from driving automobiles—if this were possible. Finally, even the latest methods of medical care of traumatic injuries will not prevent disabilities in the case of a mangled victim of a traffic accident.

From this impasse, we might conclude that it is impossible to prevent automobile accident injuries. Such is not the case. Although at present it may not be possible to prevent traffic accidents, it *is* possible, *by application of present knowledge,* to eliminate a large proportion of automobile collision injuries, disabilities and deaths.

Research in traffic accidents has revealed that two distinct and separate events occur in most traffic accidents. The first or *primary collision* occurs when the automobile hits either another automobile or the environment, that is, a roll-over or collision with a barrier. A *secondary collision* occurs fractions of a second later between the occupants of the vehicle and the interior of the vehicle, unless they are ejected. This is the collision responsible for most of the current automobile accident injury epidemic.

A recent investigation[2] of the causes of deaths of occupants of automobiles after traffic accidents revealed that the majority of victims would have survived if they had been wearing proper restraints and if the automobile had contained a few simple safety modifications—specifically, changes in the interior design, adequate interior padding, and sufficient reinforcement of the motorist compartment to enable it better to withstand crushing external forces.

The failure of preventive medicine in this situation is clear, for these are not new ideas. A report in 1954[3] from a leading automobile crash research organization stated: "It is entirely unrealistic to assume that the frequency of traffic accidents can be greatly reduced in the foreseeable future [but] with the application of reasonable and practical injury-minimizing designs and safety devices, the fate of these accident victims of the future can be remarkably improved."

Physicians must accept the responsibility for prevention and control of our latest epidemic: automobile collision injuries.

This requires the dissemination to the public of the importance of seat belts and upper torso restraints. Safety must and can be sold, including the awareness of the necessity for changes in automotive design to protect the occupants, whether or not they are wearing restraining harness.

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INFORMATION

White House Conference on Health

SEVEN HUNDRED to eight hundred leaders in medicine, public health, hospital administration, medical education, health insurance, industry, labor, government and representatives of the public attended by invitation the White House Conference on Health held 3-4 November 1965 in Washington, D.C.

George W. Beadle, president of the University of Chicago, was chairman of the conference, and Mr. Boisfeuillet Jones, formerly special assistant on health to the Secretary of HEW, was executive vice chairman.

The conference was organized into a number of general sessions and into three sequentially held panels on (1) Health Professions Education, with Dr. Lowell T. Coggeshall as chairman; (2) Health Care, under the chairmanship of Mr. Marion Folsom, formerly Secretary of HEW, and (3) Health Protection, with Dr. Leona Baumgartner chairman.

The general sessions were addressed by, among others, John W. Gardner, Secretary of HEW, Dr. Philip R. Lee, Assistant Secretary for Health and Scientific Affairs, Dr. William H. Stewart, Surgeon General of the US Public Health Service, Senator Lester Hill, Representative John E. Fogarty, Secretary of State Dean Rusk, Dr. Marcolino G. Candau, Director General of WHO, Dr. James Z. Appel, President of the American Medical Association, and Dr. Philip Bonnet, president of the American Hospital Association.

Medicine in California was represented on the program by Drs. E. Grey Dimond, La Jolla; Roger Egeberg, Los Angeles; Cecil C. Cutting, Oakland; Malcolm S. M. Watts, San Francisco; Lenor S. Goerke, Los Angeles, and Dwight L. Wilbur, San Francisco, member of the Executive Committee and moderator of the panel on Quality of Health Care. Dr. Ralph Teall and Dr. Samuel R. Sherman were invited guests.

The AMA was represented by Dr. Appel, who spoke at a general session, by Dr. W. Clarke Wescoe, moderator of a panel on Trends in Continuing Professional Education, by Dr. Raymond L. White, consultant in socioeconomics to the Executive Vice President of the AMA, who as a panel member spoke on "Practitioners and Health Care Planning," and by Dr. Wilbur, also a panel moderator. Dr. Charles L. Hudson, President-Elect, and Dr. F. J. L. Blasingame, Executive Vice President, were invited guests.

The purpose of the conference in the words of President Johnson was, "to bring together the best minds and boldest ideas to deal with the pressing health needs of this nation."

This was a conference for the development, exposure and interchange of ideas and not for action. No resolutions were made, no action taken.

Summary of the Panels

Panel on Health Professions Education. There was a spontaneous consensus that present methods of developing health manpower are insufficient and inadequate and that the same applies to current organization and methods for delivery of health services. Incentives to attract all people, including the underprivileged, to the health field must be developed (this includes youth of low income families). Disadvantaged people might achieve useful and productive employment in the health field even though not qualified for professional education.

Lack of a single unifying force in health professions education was recognized. Analysis and realization of the skills and knowledge needed by various branches of the health professions is essential, for then tailor-made educational programs can be established within the same institution so that they will become true centers of composite training rather than individual islands developing single competencies. Educational institutions must become the centers of education for all health professions. Joint education of primary and ancillary specialists is needed, with both horizontal and vertical mobility. Support of education and health manpower is an integral part of the cost of health care. There is need to develop adequate guidelines for financing services provided by medical schools.

The role of the health team requires better definition. How is it constituted, what types of training are necessary, what are the costs involved, what is the effect of team approach on health? There is an urgent need for careful analysis of the skills and knowledge needed by each allied health worker and a particular need to expand the concept of the physician assistant, health visitor, community health aid—call him what you will. One means for acquiring the necessary data regarding the health team and the "community health aid" to permit planning for the future would be to establish community models that will explore the relationships of the various health fields. Community-based and strongly tied to community and university hospitals, these would be centers of operations research, for community education and for continuing education in health professions, and at the same time would provide necessary services particularly for attacking those diseases of multiple etiology—true preventive medicine.

Such units will be successful only if there is a major commitment by the health professions through their professional schools and societies, a major commitment of funds through private and public sectors and a major commitment of all educational institutions to cooperate for the public benefit.

The demand for medical services will increase, the available health manpower will be severely strained, more and more decisions will have to be made with the community benefit in mind in order to provide the best health care available to all people at any time in a convenient place. Knowledge of costs and of what staffs are needed must be known so that our educational institutions will retool to train the necessary manpower.

Universities will have to assume the role of catalytic agent, move into new areas and cooperate with all other educational institutions and groups within the community. They will have to take on jobs that had been restricted to professional societies and associations in private groups and local organizations. In order to accomplish its role in teaching, the university must take the primary lead in developing and providing the necessary education and training. The university must have firm financial support as well as the cooperation of the health professions.

For maneuverability in the use of funds, it is necessary to constantly strive to maintain a proper balance between public and private financing so the university can underwrite the innovative programs necessary to broaden and improve the quality of education for health services.

Education for the health field is big business. Not money alone but careful planning for intelligent and prudent use of available monies is necessary.

The American people are prepared to pay more for the kind of health services they demand and they are awaiting an adequate plan.

Panel on Health Care. We have to develop organizational structures and provide the practitioner full access to new knowledge of the fruits of our research efforts. Comprehensive, continuous and personal care should be available for all as a basic human right. In an abundant society we have the resources, capacity and obligation to do this. The economically, culturally and physically disadvantaged are deprived of health and health care needs. We do not know enough about how to organize and deliver health service—nor do we do enough with what we know. Less than one-half of 1 per cent of health research expenditures is spent for research on the organization and delivery of health services. Every medical school should engage in health care planning with the community as a laboratory for research and demonstration of comprehensive health care.

A personal physician, whether he practices alone or in a group, should have responsibility for health care. The group arrangement has built-in peer interaction to improve quality, and the prepaid group plan has especial economic advantages. Highest quality should be the goal in planning for organization and delivery of health care, and accreditation and control of quality have to be extended beyond the confines of hospital.

Good health care is expensive and the costs of it need to be controlled. Better care can be provided by one 300-bed hospital than by an equal number of beds in smaller and less well staffed and equipped institutions.

The nation's health bill will continue to rise. Health insurance must be expanded and extended. We must suit our insurance schemes to comprehensive care available at hospital, out patient departments, office and home.

Planning is urgently needed now within communities, between federal and local agencies and between private and public sectors for the efficient and economic use of a growing portion of the Gross National Product devoted to health. Broad public involvement and support of the planning process makes implementation easier. But implementation will mean subordination of individual agency preference to the wider interests of the community. Leverage to service this public interest can be provided by control of finances, by franchising authority and by the legislative process.

Patterns in Hospital Use

PARTIAL RESULTS OF A STUDY IN MASSACHUSETTS

A Report of the Bureau of Research and Planning, California Medical Association

RECENTLY PUBLISHED partial results of a study of hospital admissions in the State of Massachusetts provide information on reasons for admission to 50 hospitals studied, and possible alternative sites of treatment, as reported by admitting physicians.*

For 3, 4 and 8 per cent of the medical, surgical, and diagnostic admissions, respectively, the physicians interviewed regarding a sampling of cases stated that treatment "could be done as well outside the hospital."

For 2, 5 and 8 per cent of the surgical, medical and diagnostic admissions, respectively, the physicians replied that they "normally do not recommend hospitalization" for the cases they admitted.

These and other data regarding alternatives to hospitalization provide clues as "to what extent the hospital admission and discharge system can be modified and tightened . . . ," according to Odin W. Anderson, Ph.D., Professor and Research Director of the Health Information Foundation.

In commenting on the preliminary results of the study of 2,355 hospital discharge cases in the State of Massachusetts, Dr. Anderson said:

"It should not be surprising that physicians revealed that an appreciably large minority of patients did not 'absolutely' have to be in the hospital, because medical care has expanded far beyond life-saving and emergency standards. It has built into its standards of practice a relatively large margin of safety, comfort, and convenience, reflecting the affluence of the economy itself. Certainly it can be assumed that hospital use can be cut back a great deal without endangering life, and this study can give us some idea of the areas of use that can be cut back if we simply wish to tighten the system and save money. It should be remembered that this study does not measure the volume of needed hospital care that was not being sought by the population. There is a consensus that if even by gross standard all needs were to be fully met, hospital use would have to rise."

In addition to the data cited above, the survey revealed that for 7, 14, and 15 per cent of the surgical, medical, and diagnostic admissions, respectively, alternative sites of treatment were "possible but less satisfactory outside of hospital." With regard to the physician's normal practice in recommending hospitalization, those interviewed stated that, for 14, 18, and 26 per cent of the surgical, medical, and diagnostic admissions, respectively, they "sometimes insist on hospitalization, sometimes do not."

Table 1 lists the reasons given by physicians as to why diagnostic admissions were made, even though these physicians said that their patients might have been handled otherwise. It should be noted that a total of 55 per cent of all patients admitted for diagnostic purposes could be num-

TABLE 1.—*Reasons for Admission of Patient to Hospital for Diagnostic Tests Which "Might Have Been Done Outside," Massachusetts, 1960-1961*

Reason Given	*Per Cent Answering*
Patient too ill to have them done outside	11
Medical treatment also required	21
Needed many, frequent, complex tests	39
Surgery anticipated	6
Hospital laboratory facilities superior	12
Age, location, history, condition of patient	7
Personality of patient	7
Patient preferred tests in hospital	3
Home situation unsatisfactory	5
Miscellaneous	17
Don't know	4
	132%

TABLE 2.—*Alternatives for Treatment of Those Patients for Whom Hospital Admission Was Not "Absolutely Necessary," Massachusetts, 1960-1961*

Alternatives	*Per Cent Answering*
Keep patient on medicine or treatment	13
Some medical appliance or contrivance	5
Care or treatment at home	19
Care or treatment in office or outpatient department	18
Do nothing, hope it will not get worse	5
Do nothing, put up with pain, discomfort, recurrence	11
Do nothing, put up with impairment	8
Nothing, no alternative, only postpone it	17
Miscellaneous	1
Don't know, vague	6
	103%

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*Health Information Foundation: *Progress in Health Services,* Vol. XIV, No. 1, January-February, 1965.

bered among this group. (Since multiple reasons were often given per cents shown in Table 1 exceed 100.)

Table 2 lists the reasons given by physicians for the 30 per cent of all admissions which were not deemed "absolutely necessary," and for which the admitting physicians were asked what alternatives there would have been other than hospitalization or surgery at that time. This 30 per cent includes respondents who indicated that patients would be "much better off," that hospitalization "might be a good idea," and those who either recommended against hospitalization or did not indicate a recommendation. (Per cents again total over 100 due to multiple reasons given.)

As Anderson states, "It would seem that there is no such thing as a 'pure' medical decision or a 'pure' social decision to hospitalize. If the decision were based on purely medical reasons, it would seem that a physician would be admitting a disease to the hospital and not a person with a disease. If the decision were purely social, i.e., for the physician's and patient's convenience, only the patient might then just as well be placed in a good hotel near the physician's office. Such are the issues that emerge from this survey."

Although no generalizations can be made about the data, since they pertain to practices of physicians in only one state, the Bureau of Research and Planning considers them to be of considerable significance in view of current discussion of what constitutes the "proper" use of hospitals, and the appropriateness of the hospital as the locus of treatment. The data suggest, further, the importance of creating hospital utilization and review committees in order that acceptable criteria may be established for a determination of the appropriateness of, and alternatives to, hospitalization. The adoption by individual hospitals in California of the *Guiding Principles for Physician-Hospital Relationships* (initiated by the California Medical Association and adopted by the California Hospital Association) provides assurances that such a committee is operative; the criteria such utilization committees develop, and the review techniques employed, can be of great value to other hospitals throughout the state and nation.

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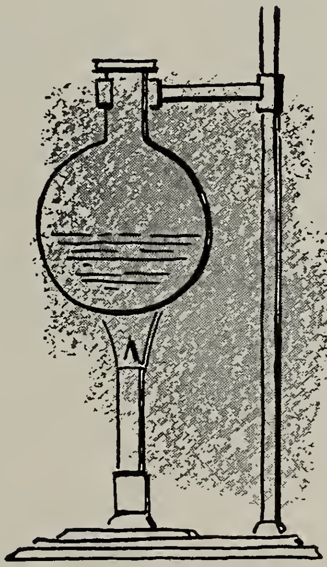

California Medical Association

Continuing Medical Education

A Proposal

ROY COHN, M.D.

Associate Dean, Graduate and Postgraduate Affairs, Stanford University School of Medicine

AN ENORMOUS EFFORT has been put forth by various medical societies, both general and specialist, throughout the country in the field of continuing medical education. Similarly the California Medical Association has been vitally interested and has spent large amounts of time and money in an attempt to find some solution to this problem.

My own impression is that the programs as presently organized do not solve the basic problem in continuing education of the physician. One-day intensive meetings on the campus of the various medical schools, or the tours which are organized through the various valleys, or the institutes which last 2 to 3 days attract a certain per cent of the practicing profession. Usually those individuals who attend this sort of thing with regularity are the ones who are interested in continuing learning and probably would obtain this same information if none of these particular programs existed. That large percentage of practicing physicians, however, who never attend these meetings are unapproachable by any present method of continuing education. The problem is not so difficult when one is dealing with the specialist's meeting, but it becomes extremely difficult when one is attempting to cover an audience made up of persons who have widespread interests and backgrounds.

When attempts have been made to evaluate what is obtained from these various courses, there is considerable evidence to support the disconcerting conclusion that very little is actually retained. The attempts to bring education to the man who will not come to the campus or attend a formal meeting by presenting educational programs through television and radio have produced equally dubious results. I would agree completely with the position taken by Dr. George E. Miller, Director of Research and Medical Education, University of Illinois College of Medicine, speaking at the 7th Annual Meeting of the Council on Medical Television at the University of Michigan last May. Responding to a glowing account of the prospects in the "Communications Bonanza," he pointed out that "equipment is not education" and that emphasis on devices for *teaching* are deflecting us from an understanding of the processes of *learning.* I call to your attention as well the skepticism registered by Dr. Stanley J. Wolfe, Director of Medical Education, St. Luke's Hospital, San Francisco at CMA's conference last fall on coordination of continuing medical education, in which he expressed serious reservations about the efficacy of traditional programs of continuing medical education, and particularly of gadget methods of teaching.

To me the only solution of this learning problem is to make it the responsibility of the schools of medicine and to solve the problem in the same way that the student and house staff problems have been solved. That is, the physician must return to school and to the bedside at the school. Therefore, the course which he takes must extend over a much greater period of time than is covered in the present courses.

Each medical school should be responsible, department by department, for taking on a number of men in practice, providing them with a temporary position on its faculty or house staff commensurate with their background, and place them once more in the time-honored position of learning from the bedside, consulting with faculty especially interested in the patient's particular problem, and having the opportunity to attend conferences, to read in the library, unhampered by the problems of his office. And each

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medical school should be obliged to take on only that number of physicians suitable to its facilities and faculty interests.

Obviously this will mean a considerable sacrifice of time and money on the part of the physician. It is here, perhaps, that the federal government may enter into the picture to subsidize these men who are adding to their own education for the general good. So far efforts on our part to obtain subsidization for this form of training have met with many comments of interest but no financial backing.

PROPOSED PROGRAM

Purpose

This program—which is not in effect—is suggested for the purpose of providing educational opportunities to physicians and specialists in the practice of medicine in all its clinical fields. It is directed especially at those men who have been in practice ten years or more and whose place of practice is away from the university medical center. It is designed to offer to these men a more intimate contact with the recent scientific advances applicable to clinical medicine.

Training Plan

Category 1 (specialists). Subject to the approval of the appropriate department chairman, sufficiently well-trained personnel who had been in the practice of medicine for approximately ten years would be given a three- to six-month temporary faculty appointment in the department of his choice. During this period he would be assigned the regular duties of any other instructor in the department with adequate time for seminar attendance and library work.

Category 2 (generalists). For the less specialized individual in practice similar opportunities would be offered except that these individuals would be listed as residents with the duties of the resident but in a more limited work load so that their patient exposure would be in depth and at the pace at which they wished to pursue it.

Category 3. Any physician in practice in the state of California could, under the following circumstances, study in depth his patient. This would be done in the following manner. Let us say that a physician, presumably a generalist in Dunsmuir, has two patients with obscure dermatological lesions which he would like to refer to a specialist. He would arrange with the chief of service to admit these patients to the service. He would then come down for the week or ten days which those patients were in the hospital and would act as the resident on that service for those patients. Thus he would write up the history and physical examinations, order the laboratory work, and study the patient under the consultant's guidance just as if he were a regular member of the staff. He could make whatever arrangements he wished with the patient as far as fees were concerned. As long as the patient paid his hospital bill and a consultation fee for the dermatological service, we would be concerned no further. When the patients were discharged, the doctor would leave, returning to the community and following the patients from then on in his office. The experience would allow the patient to receive expert care, would allow the doctor to study his patient in depth under expert guidance, and yet would take up considerably less of the doctor's time under categories 1 and 2.

Categories 1 and 2 would be allowed $500 per month while in training. Participating departments at Stanford, if such a program could be organized, would be Medicine, Surgery, Radiology, Obstetrics and Gynecology, Psychiatry, and Pediatrics. Each department could accept one man in each category per month. Minimum time required would be two months, with extension if desirable. Attempts to provide a resident as a locum tenens would be considered.

As yet no financial support for the above program has been obtained.

REQUEST FOR SCHEDULE CLEARANCE OF CONTINUING MEDICAL EDUCATION
and listing in CALIFORNIA MEDICINE and *Medical Dates Bulletin*
(deadline: fifth of the preceding month)

FROM: ______________________________________
(Organization) (Address)

My organization plans to offer a medical meeting or postgraduate course. Details are listed below. Please send me information on other meetings scheduled:

______________, ______________, ______________,
(week or month) (subject) (location)

so that we can avoid unnecessary conflict or duplication.

- -

Name of course or meeting ______________________
Time and Date(s) ______________ Place ______________
Principal subject(s) ______________________
(Please forward a copy of the program to CMA when it is ready)
Number of hours of instruction ______________ Fee, if any ______________
This course or meeting is scheduled annually: Yes ____ No ____
If yes, please give specific dates and locations for: Next year ________, ________
Second year ________, ________ Third year ________, ________
Invitations to attend extended to: ______________________
(Field or specialty) (Geographical area)
Contact for information: ______________________
(Name and title) (Address)

Describing "Subjective Disability"

THE SEMANTIC SYSTEM

On 26 June 1956 the Industrial Accident Commission adopted "Definitions of Subjective Disability," which are used to determine permanent disability ratings (and their monetary equivalents) for subjective complaints. Consequently, it is imperative that the physician use accurate terminology when describing such disabilities. Subjective disability can best be evaluated by:

1. A description of the activity which the patient alleges he cannot carry out because of the disability.
2. The duration and extent of the disability.
3. Those activities which the disability precludes, and those which it permits.
4. The means necessary for relief.

The following definitions have been developed by the Commission:

1. A *minimal* pain would constitute an annoyance, but would cause no handicap in the performance of the particular activity, and would not entail a disability rating.
2. A *slight* pain could be tolerated but would cause some handicap in the performance of the activity precipitating the pain.
3. A *moderate* pain could be tolerated but would cause marked handicap in the performance of the activity precipitating the pain.
4. A *severe* pain would preclude the activity precipitating the pain.

If the word *minimal* is used, no rating is entailed, but when it is changed to *slight,* even on strenuous work, a rating is given. The rating is increased as soon as the occasional *slight* pain becomes constant.

Back disabilities are not scheduled ratings but are based on judgment. The chart below provides some examples of the various percentage ratings (and their equivalent in dollars) in permanent disability awards.

8%—$1,700 range	Constant minimal to slight pain in the low back, aggravated by bending and repeated stooping.
10%—$2,200 range	Constant slight pain in low back during work activity. Constant slight, dull aching over back with occasional momentary sharp pain; very occasional burning sensation in thighs while working.
15%—$3,300 range	Low back disability precluding work involving very heavy lifting. Constant slight pain in lower back, precluding heavy work such as carrying heavy trays while waiting on tables.
30%—$6,600 range	Constant slight pain in low back preventing applicant from doing heavy work. Constant aching pain over neck and back, aggravated by motion such as lifting and stooping, precluding heavy work.
40%—$8,800 range	Constant slight to moderate pain in lower back, preventing heavy lifting (over 35 lb.) or walking more than one mile.
50%—$11,000 range	Moderate to severe pain in cervical and lumbosacral spine, limiting applicant to light work.
70%—$15,000 range	Low back and lower extremity disability, precluding work except of a sedentary nature.

When it is realized that the Commission could (under existing law, conflict of medical testimony, and/or interpretation of weight of medical evidence) permit a rating of 100 per cent based on subjective disability alone, the need for careful evaluation of an applicant's subjective complaints as related to his medical history and physical findings, becomes apparent.

COMMITTEE ON OCCUPATIONAL HEALTH
CALIFORNIA MEDICAL ASSOCIATION

16th ANNUAL regional postgraduate institute

EL MIRADOR HOTEL
Palm Springs
February 3-4, 1966

SOUTHERN COUNTIES

Presented cooperatively by Southern Counties Medical Societies, University of Southern California School of Medicine, and the Committee on Continuing Medical Education, California Medical Association. A 12-hour course.

HOST: Riverside County Medical Association
***Regional Chairman:* Robert M. Zweig, M.D., 3875 Jackson, Arlington.**

INSTITUTE FEE: $15.00. For additional information contact Continuing Medical Education office, California Medical Association, 693 Sutter Street, San Francisco 94102. All California Medical Association members and their families are cordially invited to attend.

PROGRAM THEMES:

CARDIOVASCULAR DISEASE . . . ANTIBIOTICS AND INFECTIOUS DISEASES . . . HEMATOLOGY

THURSDAY, FEBRUARY 3

8:15—**Registration**

Morning Session

9:00-9:30—**Recent Advances in the Treatment of Myocardial Infarction**—Professor P. A. Owren

9:30-10:00—**A Report on the Riverside Salmonellosis Epidemic**—to be announced

10:00-10:30—**Diagnosis of Anemia**—Samuel I. Rapaport, M.D.

10:30-10:45—Intermission

10:45-12:15—CONCURRENT WORKSHOPS (you may go to one of your choice):

- A. **Clinical Aspects of Atherosclerosis**—David H. Blankenhorn, M.D., Phil R. Manning, M.D.
- B. **Enteric Infections**—Allen W. Mathies, Jr., M.D.
- C. **Anemia**—Samuel I. Rapaport, M.D.

Afternoon Session

1:45-2:15—**Drug Therapy in Essential Hypertension**—Robert F. Maronde, M.D.

2:15-2:45—**Treatment of Staphylococcus Infections**—John M. Leedom, M.D.

2:45-3:15—**Drug Therapy in the Leukemias**—Jesse L. Steinfeld, M.D.

3:15-3:30—Intermission

3:30-5:00—CONCURRENT WORKSHOPS (you may go to one of your choice):

- A. **Diagnosis of Arrhythmias**—Irwin Hoffman, M.D., Phil R. Manning, M.D.
- B. **Complications Occurring with Antibiotic Therapy**—John M. Leedom, M.D., Allen W. Mathies, Jr., M.D., Paul F. Wehrle, M.D.
- C. **The Diagnosis and Treatment of Anemias**—Samuel I. Rapaport, M.D.

FRIDAY, FEBRUARY 4

Morning Session

9:00-9:30—**Classification and Mechanism of Antibiotic Action**—Allen W. Mathies, Jr., M.D.

9:30-10:30—**The Management of Hemorrhagic Diseases**—J. Philip Loge, M.D., Professor P. A. Owren, Samuel I. Rapaport, M.D., Charles H. Watkins, M.D.

10:30-10:45—Intermission

10:45-12:15—CONCURRENT WORKSHOPS (you may go to one of your choice):

- A. **The Diagnosis of Chest Pain**—David H. Blankenhorn, M.D., Phil R. Manning, M.D.
- B. **Principles of Antibiotic Selection**—John M. Leedom, M.D., Allen W. Mathies, Jr., M.D., Paul F. Wehrle, M.D.
- C. **Bleeding Tendencies**—Samuel I. Rapaport, M.D.

Afternoon Session

1:45-2:15—**The Problem of Hypercoagulability**—Professor P. A. Owren

2:15-2:45—**Arrhythmias**—Irwin Hoffman, M.D.

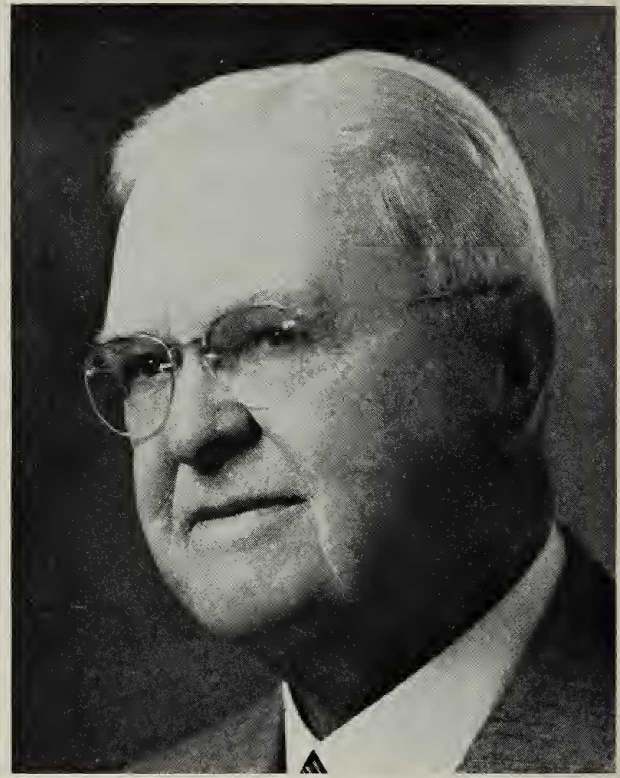
2:45-3:15—**Management of Common and Uncommon Bacterial Infections**—Paul F. Wehrle, M.D.

3:15-3:30—Intermission

3:30-5:00—CONCURRENT WORKSHOPS (you may go to one of your choice):

- A. **The Treatment of Essential Hypertension**—Robert F. Maronde, M.D.
- B. **Fever of Undetermined Origin**—John M. Leedom, M.D., Allen W. Mathies, Jr., M.D., Paul F. Wehrle, M.D.
- C. **Chemotherapy of Malignancies**—Jesse L. Steinfeld, M.D.

EDWARD NORTON EWER, M.D.



It is with particular sorrow that we report the death of DOCTOR EDWARD NORTON EWER on 17 October 1965. His long and useful life spanned more than half of this century and nearly half of the last century, a period which has been characterized by great changes in the practice of medicine, and there are few of us today who would not agree that the science of medicine (perhaps as contrasted with the art of medicine) has advanced beyond the dreams of its most imaginative practitioners. It is a privilege to have known Doctor Ewer and to have witnessed the evolution of medical practice in his time.

The man who was to become clinician, professor, medical leader and the father of two distinguished physician sons, Doctor Ewer was born in Milwaukee, Wisconsin, on 14 March 1866. He graduated from the University of Michigan in 1892 and practiced briefly in Ohio and Wisconsin before settling in Oakland in general practice in 1898. In the meantime he had studied obstetrics and gynecology in Dublin, but it was not until 1912 that he entered into his chosen specialty.

In 1906 he found himself in the midst of the disruption of the Bay Area caused by the earthquake and fire, and one of his assignments was as health officer in charge of a refugee camp on the shores of Lake Merritt, where he was confronted with isolation of a large number of smallpox patients and with an outbreak of typhoid.

Following that, he again went to Europe to study obstetrics and gynecology, this time to Germany where he studied with Doctor Franz of Munich. For many years after returning to Oakland in 1912 he was professor of obstetrics and gynecology at the Oakland College of Medicine, and many physicians in California remember him as their teacher there. After the dissolution of the college, he continued to be in the forefront of teaching and practicing this specialty of medicine.

In 1905 he was President of the Alameda County Medical Association. He was the organizer of the first section on Obstetrics and Gynecology of the CMA in 1918, and became President of the California Medical Association in 1926. Long after his term of office as President of the CMA, he continued to attend the meetings of the House of Delegates. He was a Delegate to the American Medical Association from 1941 to 1944. In 1931 he was one of the founding group of the Western Obstetrical and Gynecological Society.

He was an able practitioner, a kindly consultant, with a "no nonsense" approach to the problems of his profession.

Doctor Ewer had the hobbies of fishing and woodworking and was affectionately known throughout the area as "Daddy Ewer," having come by this sobriquet because his oldest son, John Norton Ewer, followed in his father's footsteps and located in Oakland in practice with his father in obstetrics and gynecology. John Ewer's untimely death occurred in 1960.

Doctor Ewer was a widower during the last years of his life and he is survived by his only other son, Doctor Edward G. Ewer, a distinguished orthopedic surgeon in Oakland, and four living grandchildren and nine great grandchildren.

T. ERIC REYNOLDS, M.D.

In Memoriam

JOHN HUNTON

JOHN HUNTON, 62, executive secretary of the California Medical Association for the past 25 years, died late 2 December from a heart attack suffered in his home at 155 Yerba Buena Avenue, San Francisco.

Mr. Hunton became the CMA's first executive secretary on 1 October 1940. He was the first member of the CMA executive staff to complete 25 years of continuous service. On 30 October 1965, he was honored by the CMA Council for his outstanding contributions to medicine over that period.

Mr. Hunton grew up in Evanston, Illinois. He attended the University of Nebraska, majoring in business administration, then worked for a short time in the *Chicago Tribune's* advertising department. In the early 1930's he came to San Francisco, where he joined the editorial staff of the *Wall Street Journal.* He became city editor of the *Journal.* A story he wrote on formation of California Physicians' Service so impressed CMA officers that they decided to hire him as executive secretary.

Mr. Hunton is survived by his wife, Pia; two stepsons, John Quilici, M.D., a resident physician at the University of California Medical Center, San Francisco, and Vincent Quilici, a medical student at the U.C. School of Medicine in San Francisco; a grandson, John Quilici of Burlingame, and two brothers, Frank Hunton of Illinois and Paul Hunton of Kansas.

BOERICKE, CHARLES CALEB, Berkeley. Died 4 November 1965, in Berkeley, aged 68. Graduate of Hahnemann Medical College and Hospital of Philadelphia, Pennsylvania, 1924. Licensed in California in 1924. Doctor Boericke was a member of the Alameda-Contra Costa Medical Association.

✣

BRICCA, CONSTANTINE R., San Francisco. Died 19 October 1965, in San Francisco, aged 86. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1905. Licensed in California in 1905. Doctor Bricca was a member of the San Francisco Medical Society.

✣

CALLAWAY, WILLIAM O., San Diego. Died 3 October 1965, in San Diego, aged 77. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1914. Licensed in California in 1922. Doctor Callaway was a retired member of the San Mateo County Medical Society and the California Medical Association, and an associate member of the American Medical Association. He had been a priest in the Catholic Church since 1960.

✣

CHAIS, GEORGE JOEL, Encino. Died 18 October 1965, in Encino, aged 59, of acute cerebral vascular hemorrhage. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1934. Licensed in California in 1934. M.D. degree from California College of Medicine, 1962. Doctor Chais was a member of the Los Angeles County Medical Association.

✣

COFFEY, GRUNDY C., Ventura. Died 22 October 1965, in Ventura, aged 87. Graduate of the University Medical College of Kansas City, Missouri, 1901. Licensed in California in 1923. Doctor Coffey was a retired member of the Ventura County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✣

COLBERT, JOHN WILLIAM, Los Angeles. Died 18 October 1965, in Los Angeles, aged 85, of cerebral vascular accident and uremia. Graduate of St. Louis University School of Medicine, Missouri, 1903. Licensed in California in 1914. Doctor Colbert was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

DESSER, A. LINCOLN, Los Angeles. Died 16 October 1965, in Los Angeles, aged 77, of carcinoma. Graduate of the University of Illinois College of Medicine, Chicago, 1911. Licensed in California in 1920. Doctor Desser was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Ewer, Edward Norton, Berkeley. Died 17 October 1965, in Oakland, aged 99 of arteriosclerotic heart disease. Graduate of the University of Michigan Medical School, Ann Arbor, 1892. Licensed in California in 1898. Doctor Ewer was a member of the Alameda-Contra Costa Medical Association, a life member of the California Medical Association, and a member of the American Medical Association.

◆

Franklin, Wayland R., Los Angeles. Died 5 October 1965, in Inglewood, aged 78, of malignancy of prostate. Graduate of Chicago College of Medicine and Surgery, Illinois, 1912. Licensed in California in 1917. Doctor Franklin was a member of the Los Angeles County Medical Association.

◆

Futterman, Milton Samuel, Pico Rivera. Died 7 November 1965, in Downey, aged 47, of cerebral vascular accident. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1942. Licensed in California in 1942. M.D. degree from California College of Medicine, 1962. Doctor Futterman was a member of the Los Angeles County Medical Association.

◆

Hoyt, Hubbard Spencer. Died 7 August 1965, aged 70, of coronary occlusion. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1921. Licensed in California in 1921. Doctor Hoyt was a member of the Monterey County Medical Society.

◆

Jones, William Ansel, Moorpark. Died 30 August 1965, aged 61. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1950. Doctor Jones was a member of the Ventura County Medical Society.

◆

Langsdorf, Gordon C., San Diego. Died 25 October 1965, in La Jolla, aged 52, of carcinoma of bladder. Graduate of the University of Oregon Medical School, Portland, 1938. Licensed in California in 1938. Doctor Langsdorf was a member of the San Diego County Medical Society.

◆

Nossek, Harry Joseph, Lodi. Died 7 September 1965, in Lodi, aged 74, of acute congestive heart failure. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1931. Licensed in California in 1931. M.D. degree from California College of Medicine, 1962. Doctor Nossek was a member of the San Joaquin County Medical Society.

◆

Palmer, Alfred Merle, Castro Valley. Died 28 Octomer 1965, in Castro Valley, aged 80. Graduate of the University of Colorado School of Medicine, Denver, 1911. Licensed in California in 1923. Doctor Palmer was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Prier, William E., San Luis Obispo. Died in May, 1965, aged 42. Graduate of Tufts University School of Medicine, Boston, Massachusetts, 1951. Licensed in California in 1961. Doctor Prier was a member of the San Luis Obispo County Medical Society.

◆

Rowe, Melvin John, Sr., Long Beach. Died 27 September 1965, in Long Beach, aged 85, of coronary artery disease. Graduate of the University of Michigan Medical School, Ann Arbor, 1903. Licensed in California in 1914. Doctor Rowe was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Shalit, Ivan E., Walnut Creek. Died 13 October 1965, in Walnut Creek, aged 38. Graduate of Western Reserve University School of Medicine, Cleveland, Ohio, 1959. Licensed in California in 1961. Doctor Shalit was a member of the Alameda-Contra Costa Medical Association.

◆

Shepard, Charles Edward, Palo Alto. Died 5 July 1965, aged 66, of cerebral hemorrhage. Graduate of the University of Minnesota Medical School, Minneapolis, 1924. Licensed in California in 1930. Doctor Shepard was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

CMA

ANNUAL SCIENTIFIC ASSEMBLY

MARCH 20-23, 1966

LOS ANGELES

current concepts in therapy

POINT AND COUNTERPOINT

featuring—

RENAL FAILURE
CORONARY ARTERY DISEASE
GASTROINTESTINAL HEMORRHAGE

- ***among the distinguished speakers presenting their "current concepts in therapy":***
  - CHARLES K. FRIEDBERG, M.D., Columbia University
  - BERNARD LOWN, M.D., Harvard University
  - BELDING H. SCRIBNER, M.D., University of Washington
  - OWEN H. WANGENSTEEN, M.D., University of Minnesota

A VARIETY OF EVENTS in addition to those directly related to this year's theme WILL HIGHLIGHT YOUR 1966 ANNUAL SCIENTIFIC ASSEMBLY . . . eighteen medical specialty section meetings . . . seven special conferences . . . motion picture symposia . . . color TV programs . . . scientific and technical exhibits.

application for HOTEL ACCOMMODATIONS

NINETY-FIFTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • MARCH 20-23, 1966
BILTMORE HOTEL, LOS ANGELES

House of Delegates Opening Session, Saturday evening, March 19: Scientific Programs begin Sunday morning, March 20.

---

1. Fill in the form below **completely** for room accommodations at the CMA's 1966 Annual Session. There is only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations must be made through the CMA Housing Bureau, 693 Sutter Street, San Francisco, California 94102.
4. **DEADLINE** for housing: March 4, 1966.

HOTEL ROOM RATES*

	Single	Double and Twins	Suites
BILTMORE HOTEL			
515 So. Olive Street	10.50-16.50	15.50-20.50	30.00-50.00
MAYFLOWER HOTEL			Triples
535 So. Grand Avenue	8.00-12.00	12.00-16.00	19.00
STATLER-HILTON			Suites
930 Wilshire Boulevard	10.00-17.50	16.00-22.50	30.00-65.00

*Rates subject to change

Send to: California Medical Association—*Housing Bureau*
693 Sutter Street, San Francisco, California 94102

Please reserve the following accommodations for the CMA's 1966 Annual Session in Los Angeles, March 20-23, 1966. The first meeting of the House of Delegates begins Saturday evening, March 19: Scientific Programs begin March 20.

Single Bedroom $.................... Twin-Bedded Room $.................... Double Bedroom $....................

Small Suite $.................... Large Suite $.................... Other $....................

First Choice Hotel.................... Second ....

Arrival (date) .... Hours .... a.m. p.m. Departure (date) .... Hour .... a.m. p.m.

THE NAME OF EACH HOTEL GUEST MUST BE LISTED. Include the names and addresses of both persons for each twin-bedded or double room, and names and addresses of all other persons for whom you are requesting reservations.

—PLEASE PRINT—

Your Name .... Officer? .... Delegate? .... Alternate? .... Speaker? ....

Address .... County ....

City and State .... Zip No. ....

WOMAN'S AUXILIARY

to the California Medical Association

Communication—A Necessity

EFFECTIVE communication is of vital importance as a life line to any organization. This is especially true when that organization spans a state the size of ours.

The Woman's Auxiliary to the California Medical Association, with 34 separate county units and 8,812 members, requires a liaison between national, state and county medical auxiliary activities. There is so much going on within WACMA relative to legislation, AMA-Education and Research Foundation (we led the nation in fund-raising last year), health careers scholarships, GEMS (Good Emergency Mother Substitutes), International Health Activities and so on that our membership could never be kept informed without our quarterly magazine, *The Courier*.

Our National President, Mrs. Richard A. Sutter, while attending our recent State Fall Conference at Palo Alto, strongly reaffirmed the request of AMA Auxiliary headquarters that our *Courier* be sent to all national officers and to all 50 state presidents and the state editors. She gave us a great compliment when she said: "Your publication is one of the finest in the United States. Other state auxiliaries look to it for ideas and stimulation in their areas."

Correspondence with our National Editorial Board confirms Mrs. Sutter's statement. They are greatly impressed by the accomplishments of the county auxiliaries throughout our state in those areas mentioned above, along with our outstanding leadership in planning annual Health Careers Days in several counties to benefit thousands of young people—tomorrow's leaders in medicine. Many of our county reports from *Courier* have later appeared in *M.D.'s Wife,* the journal of the national Auxiliary, which is mailed to every physician's wife in the United States.

Through *Courier* we continue to educate our members to the growing purposes and work of our organization. Each physician's wife must be well informed if she is to be a good interpreter for medicine in her community and, most importantly, if she is to work for the person closest to her—her husband.

Good public relations through friendships, not only among ourselves but outwardly in community service, is a basic concept of Auxiliary. It is hoped that this *interest* and *challenge* is created with each issue of *Courier* which your wife receives, as her sense of loyalty to the medical profession is needed. May I refer to 2nd Vice President Mrs. Kenneth J. McNiece's closing admonition from CALIFORNIA MEDICINE, July 1965, "Doctor, be interested in your wife's participation in Auxiliary."

There is a wonderful quotation from Mathew that reads, "Let your light so shine before men that they may see your good works." The State officers, through *Courier,* sincerely hope that we will continue to turn that light of incentive in the right direction to keep our members totally informed.

MRS. H. HARPER THORPE
Courier Editor
Woman's Auxiliary to the
California Medical Association

NEWS & NOTES

NATIONAL • STATE • COUNTY

MARIN

Dr. Arthur R. Ablin of San Rafael was elected president-elect of the Marin Medical Society, it was announced at the annual election meeting of the society early last month. In January, Dr. Robert L. Mills of Ross will be installed as president for 1966.

Dr. Robert F. Schell, San Rafael, was reelected secretary-treasurer.

SAN FRANCISCO

Dr. Samuel R. Sherman, San Francisco, former president of the California Medical Association and now chairman of the Bureau of Research and Planning, has been appointed by President Lyndon B. Johnson to the 16-member Health Insurance Benefits Advisory Council. The Council will help in the formation of Government policies for operation of the new Medicare program.

Dr. Sherman is chairman of both the Council of Legislative Activities and the Council on Economics of Medical Care of the American Medical Association.

GENERAL

Beginning in January, **CPS-Blue Shield programs for Employees of the State of California** will pay usual, customary and reasonable fees to Physician Members for covered services when the employee's family income is more than $7,500 annually. Payments for employees with less than $7,500 annual income will be based on the 1964 Relative Value Studies with a $5 unit value (CPS Schedule 4D).

The State Employees group makes up one of the largest single segments of CPS-Blue Shield membership, approximately 86,000 persons, including both employees and their families.

Simultaneous with the introduction of the new professional coverage, the California State Employees Association plan which has been written by CPS for nearly 25 years is being merged with the joint Blue Cross-Blue Shield plan endorsed and sponsored by the State Employees Retirement System. Under the new arrangement, state employees will have Blue Cross hospital benefits and Blue Shield professional coverage. State employees will be offered two levels of Blue Cross-Blue Shield coverage. However the professional services covered will be the same for both. The differences between the "standard service" and "partial service" plans are in hospital coverage.

The upgrading of the professional coverage for state employees culminates months of effort. For several years CPS has been progressively improving the coverage held by this group, and first introduced the $5 unit fee schedule more than two years ago. Up until this time, however, the state has retained a "low option" professional coverage as well as the "high option" with the $5 unit conversion. CPS intensified its efforts during the past year to persuade the state of the mutual advantages of upgrading the coverage. Through these efforts the contract was renegotiated to include the plan paying usual and customary fees on behalf of upper income employees.

* * *

Deadline for submitting manuscripts for this year's **William Osler medal** of the American Association for the History of Medicine is 23 March 1966. The medal awarded for the best unpublished essay on a medicohistorical subject written by a student in one of the medical schools in the United States or Canada. All students who are candidates for the degree of Doctor of Medicine, or who graduated in 1965, are eligible.

Essays should demonstrate either original research or an unusual appreciation and understanding of a medicohistorical problem. Maximum length is 10,000 words. The prize-winning essay will be submitted to the Editorial Committee of the Association, which may recommend it for publication in the *Bulletin of the History of Medicine.*

Essays must be submitted, before the deadline, to the chairman of the Osler Medal Committee, William K. Beatty, librarian and professor of medical bibliography, Northwestern University Medical School, 303 East Chicago Avenue, Chicago 60611.

"Immunization—Your Insurance for Good Health" is a new bi-lingual pamphlet available through the California Medical Association's Commission on Community Health Services.

"The Committee on Rural Health prepared the pamphlet with migratory farm workers particularly in mind," according to Dr. Leo Snyder of Fresno, committee chairman. "It is printed in English on one side, and in 'shirt-sleeve' Spanish on the other," he said.

A history of immunization, information about record keeping and the effects, types and value of immunization are included in the pamphlet. A chart gives the recommended age to start immunization, number of dosages, intervals between them and other pertinent information.

The pamphlet is available from the CMA, 693 Sutter Street, San Francisco 94102.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts
for Postgraduate Course Information

CMA:	**California Medical Association** For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. PRospect 6-9400, Ext. 68.
LLU:	**Loma Linda University** For information contact: W. F. Norwood, Ph.D., Assistant Dean and Chairman, Division of Continuing Education, Loma Linda University School of Medicine, 1720 Brooklyn Ave., Los Angeles 90033, ANgeles 9-7241, Ext. 214.
PRES. MED. CTR.	**Presbyterian Medical Center** For information contact: Arthur Selzer, M.D., chairman, Education Committee, Presbyterian Medical Center, Clay and Webster Streets, San Francisco 94115. WEst 1-8000.
UCLA:	**University of California at Los Angeles** For information contact: Charles R. Smart, M.D., Assistant Director, Continuing Education in Medicine and Health Sciences, UCLA Medical Center, Los Angeles, 90024, 478-9711, Ext. 2114.
UCSF:	**University of California, San Francisco** For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, University of California Medical Center, Room 565-U, San Francisco 94122, 666-1692.
USC:	**University of Southern California** For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, USC School of Medicine, 2025 Zonal Ave., Los Angeles 90033, 90033, CApital 5-1511, Ext. 300.
STAN:	**Stanford University** For information contact: Roy Cohn, M.D., Associate Dean for Graduate Affairs, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto, DAvenport 1-1200.

JANUARY

January 6—**Psychiatric Evaluation: The Patient and the Family.** USC in Bakersfield. Thursday evenings. $35.

January 8—**Human Development and Birth Defects.** UCSF at Childrens Hospital, San Francisco. Saturday. 5½ hours. $15.

January 14-16—**A Time for Decision: The Biologic Crossroad.** UCSF. Friday-Sunday.

January 15—**Conference on Neurologic Evaluation.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 17-21—**Annual Mid-Winter Convention in Ophthalmology and Otolaryngology.** Statler Hilton Hotel, Los Angeles. Monday-Friday. Contact: Norman Jesbere, M.D., secretary treasurer, Research Study Club of Los Angeles, 1136 West Sixth Street, Los Angeles 90017.

January 18-April 12—**Medical Radio Conferences.** UCSF. Tuesdays, 12:30-1:30 p.m.

January 19—**Los Angeles County Heart Association Annual Midwinter Symposium.** Statler Hilton Hotel, Los Angeles. Wednesday. 6 hours. Contact: Professional Symposium Committee, 2405 W. Eighth Street, Los Angeles 90057.

January 19—**Riverside County General Hospital Postgraduate Assembly.** Riverside County General Hospital. Wednesday. 12 hours. Contact: Harold A. Roth, M.D., Riverside County General Hospital, 9851 Magnolia Avenue, Riverside 92503.

January 19-April 20—**Psychotherapeutic Principles and Practice for Non-Psychiatrists.** UCSF. Wednesdays. 70 hours. $25.

January 19-May 18—**Teaching Clinics in Psychiatry.** UCLA. Wednesdays.

January 20-21—**New and Old Antibiotics.** USC. Thursday-Friday.

January 20-April 7—**Medical Radio Conferences.** UCSF. Thursdays, 12:30-1:30 p.m.

January 22—**Central Mission Trails Heart Association Annual Symposium on Cardiovascular Disease.** Fort Ord Army Hospital, Fort Ord. Saturday. 8 hours. $10. full day, $5. half day. Contact: Donald M. Scanlon, M.D., P.O. Drawer 4948, Carmel.

January 22—**Pediatric Cardiology Symposium.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 28—**Nuclear Medicine.** USC. Friday.

January 28-30—**Clinical Conference in Pediatric Anesthesiology.** Friday-Sunday. Contact: M. Digby Leigh, M.D., Childrens Hospital of Los Angeles, 4614 Sunset Blvd., Los Angeles 90027.

January 28-30—**Dermatologic Pathology.** USC at El Mirador Hotel, Palm Springs. Friday-Sunday.

January 29—**Practical Proctology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

January 31-February 1—**Uroradiology.** UCLA. Monday-Tuesday.

FEBRUARY

Februrary 1-March 22—**Isotope Techniques in the Health Sciences.** UCSF. Tuesdays.

February 1-April 19—**Bedside Cardiology.** USC at Los Angeles County Hospital. Tuesdays.

February 2-4—**Aviation Medicine Seminars.** UCSF at Del Webb's Townehouse, San Francisco. Wednesday-Friday.

February 3-4—**SOUTHERN COUNTIES—Regional Postgraduate Institute presented by California Medical Association** in cooperation with USC School of Medicine. El Mirador Hotel, Palm Springs. Thursday-Friday "Hematology and Infectious Diseases and Antibiotics." Chairman: Robert M. Zweig, M.D., 3875 Jackson, Arlington.

February 4-5—**New Potentials in Diagnosis and Treatment.** UCSF. Friday-Saturday. 12½ hours. $40.

February 4-March 11—**Psychiatry in Daily Practice.** UCSF at Mercy Hospital, Redding. Fridays.

February 7—**Medical Aspects of Well Being: Emotional Aspects of Rehabilitation.** UCSF. Monday.

February 7-March 14—**Contra Costa County Heart Association Postgraduate Course for Physicians.** John Muir Hospital, Walnut Creek. Mondays. 12 hours. $15. Contact: Loyse C. Casebolt, executive director, 1541 East St., Walnut Creek.

February 9—**Circulatory Shock.** USC at Sheraton-West Hotel, Los Angeles, Wednesday. 8:30 a.m.-4:45 p.m. $25.

February 10—**Los Angeles Pediatric Society Annual Parmelee Memorial Lecture.** Los Angeles County Medical Association Building, 1925 Wilshire Blvd., Los Angeles. Thursday. 6:30-9:30 p.m. Contact: Paul F. Wehrle, M.D., program chairman, 9209 6th Ave., Inglewood 90305.

February 10-11—**Symposium on Endocrinology.** USC at Statler Hilton Hotel, Los Angeles. Thursday-Friday.

February 10-12—**The Specialties in Pediatric Office Practice.** UCSF. Thursday-Saturday.

February 11-13—**American College of Physicians, Northern California and Nevada Regional Meeting.** Mark Thomas Inn, Monterey. Friday-Sunday. 10 hours. Contact: Roberto F. Escamilla, M.D., Governor, Northern California and Nevada Region, American College of Physicians, 897 Hyde Street, San Francisco.

February 12—**Surgical Emergencies.** Pres. Med. Ctr. Saturday. 8 hours. $30.

February 12-13—**Cystic Fibrosis.** UCLA. Saturday-Sunday.

February 12-13—**A Symposium on Hypnosis.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

February 12-13—**Law-Science-Medicine.** UCSF. Saturday-Sunday.

February 14-16—**Institute for Metabolic Research Dynamics of Endocrine and Metabolic Disease Annual Symposium.** Highland Hospital. Monday-Wednesday $30. Contact: L. W. Kinsell, M.D., director, Institute of Metabolic Research, 2701 14th Ave., Oakland.

February 14-18—**American College of Chest Physicians —Clinical Application of Cardio-Pulmonary Physiology.** Ambassador Hotel, Los Angeles. Monday-Friday. Contact: Alfred Goldman, M.D., program chairman, Suite 906, 9201 Sunset Blvd., Los Angeles 90069.

February 14-18—**Course for Physicians in General Practice.** UCSF at Mt. Zion Hospital, San Francisco. Monday-Friday.

February 16-20—**Controversial Areas in Surgery.** UCLA at Palm Springs. Wednesday-Sunday.

February 18-19—**Pediatric Dermatology.** UCSF. Friday-Saturday.

February 18-20—**American College of Physicians Southern California Regional Meeting.** Biltmore Hotel, Santa Barbara. Friday-Sunday. Contact: W. Philip Corr, M.D., governor, 3660 Arlington Ave., Riverside 92506.

February 19-20—**Neuropsychiatry in Daily Practice.** UCSF in Salinas. Saturday-Sunday.

February 20-23—**Current Concepts in Chemotherapy.** UCLA at Palm Springs. Sunday-Wednesday.

February 24-25—**Medical-Surgical Gastroenterology Conference.** USC. Thursday-Friday.

February 25-26—**Workshop on Hand Injuries.** Pres. Med. Ctr. Friday-Saturday. 12 hours. $75.

February 25-27—**Conference on Mental Retardation for Physicians.** UCSF. Friday-Sunday.

February 27-March 2—**Surgical Applied Anatomy.** LLU. Sunday-Wednesday. 29½ hours.

MARCH

March 2-3—**Los Angeles County Heart Association Annual Spring Symposium.** Statler Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hours. Contact: Professional Symposium Committee, 2405 W. Eighth Street, Los Angeles 90057.

March 2-3—**Western Electroencephalography Society Annual Meeting.** Hilton Hotel, San Francisco. Wednesday-Thursday. Contact: Edward E. Shev, M.D., secretary treasurer, 516 Sutter St., San Francisco.

March 2-4—**American Medical Association Air Pollution Medical Research Conference.** Ambassador Hotel, Los Angeles. Wednesday-Friday. Contact: Air Pollution Medical Research Conference, Department of Environmental Health, AMA, 535 N. Dearborn St., Chicago, Illinois 60610.

March 3-4—**Symposium on Diabetes.** USC at the Ambassador Hotel, Los Angeles. Thursday-Friday.

March 4-5—**Gynecological Problems for the Non-Gynecologist.** UCSF. Friday-Saturday.

March 4-5—**Operable Heart Disease.** Pres. Med. Ctr. Friday-Saturday. 16 hours. $35.

March 5-6—**The Knee.** UCLA. Saturday-Sunday.

March 5-6—**Sex Education and the Family Doctor.** UCSF at Herrick Hospital, Berkeley. Saturday-Sunday.

March 9-11—**Conference on Keratoplasty.** Pres. Med. Ctr. Wednesday-Friday. 21 hours. $125. Contact: Lions Eye Foundation, Pres. Med. Ctr., 2018 Webster St., San Francisco 94115.

March 9-13—**Diagnostic Radiology.** UCSF. Wednesday-Sunday.

March 10—**Symposium on Obesity.** USC at the Ambassador Hotel, Los Angeles. Thursday.

March 10-14—**Pulmonary Problems.** UCLA. Thursday-Sunday.

March 11-12—**Childrens Hospital Medical Center Annual Postgraduate Seminar and Clifford D. Sweet Lecture.** Childrens Hospital, 51st and Grove Streets, Oakland. Friday-Saturday. 16 hours. $30 for 4 sessions or $10 per session. Contact. Miss Inetta Carty, Medical Staff Office, Childrens Hospital Medical Center, Oakland.

March 11-12—**WEST COAST COUNTIES—Regional Postgraduate Institute presented by California Medical Association** in cooperation with UCSF. Ojai Valley Inn, Ojai. Friday-Saturday. "Indications for Surgical Intervention—The Difficult Decision." Chairman: George J. Wittenstein, M.D., 2235 Castillo, Santa Barbara.

March 12—**Cancer: Childhood and Adult Tumors.** UCSF at Childrens Hospital, San Francisco. Saturday.

March 12—**Obstetrics and Gynecology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

March 12-13—**Neuropsychiatry in Daily Practice.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

March 13-17—**Alumni Postgraduate Convention, LLU.** Mar. 13-14 (Sunday-Monday)—Refresher Courses. White Memorial Medical Center. Mar. 15-17 (Tuesday-Thursday)—Scientific Assembly. Ambassador Hotel, Los Angeles. Contact: Samuel H. Fritz, M.D., general chairman, 1832 E. Michigan Avenue, Los Angeles 90033.

March 16—**Annual Postgraduate Symposium on Heart Disease.** O'Connor Hospital, San Jose. Wednesday. $15., incl. lunch. Contact: William G. Allayaud, executive director, Santa Clara County Heart Association, 1961 The Alameda, San Jose 95126.

March 16—**Symposium on Obesity.** USC. Wednesday.

March 19—**Catecholamines and Adrenergic Blocking Agents.** Sponsored by the American College of Cardiology and USC. Ambassador Hotel, Los Angeles. Saturday. Members: $20., Non-Members: $25. Contact: Executive Director, American College of Cardiology, 9650 Rockville Pike, Washington, D.C. 20014.

March 19—**Rheumatic Diseases.** Pres. Med. Ctr. Saturday. 8 hours. $30.

March 19-20—**California Radiological Society Annual Meeting.** Biltmore Hotel, Los Angeles. Saturday-Sunday. Contact: L. H. Garland, M.D., 450 Sutter Street, San Francisco.

March 20—**American College of Chest Physicians California Chapter Annual Meeting.** Biltmore Hotel, Los Angeles. Sunday. Contact: M. Rosenblatt, M.D., program chairman, County of Los Angeles Health Department, 220 North Broadway, Los Angeles 90012.

March 20-23—**CALIFORNIA MEDICAL ASSOCIATION 95th Annual Session.** Scientific theme: "CURRENT CONCEPTS IN THERAPY: Coronary Artery Disease. Gastrointestinal Hemorrhage. Renal Failure." Biltmore Hotel, Los Angeles. Sunday-Wednesday. Contact: Mr. John Hunton, executive secretary, 693 Sutter Street, San Francisco 94102.

March 25-27—**Postgraduate Assembly in Anesthesiology.** Sponsored by the Anesthesia Section, Los Angeles County Medical Association. International Hotel, Los Angeles. Friday-Sunday. 12 hours. $25. Contact: Thomas W. McIntosh, M.D., secretary, Postgraduate Committee, 686 East Union Street, Pasadena.

March 25-27—**Sex Disorders in Clinical Practice.** UCSF. Friday-Sunday.

March 26—**Endocrinology.** Pres. Med. Ctr. Saturday. 8 hours. $30.

March 29-30—**Southwestern Pediatric Society.** Statler Hilton Hotel, Los Angeles. Tuesday-Wednesday. Contact: Phillip Sturgeon, M.D., 1200 S. Vermont Avenue, Los Angeles 90006.

APRIL

April 1-2—**Contrast Media in Abdominal Disease: A Program for the Practicing Physician.** UCSF. Friday-Saturday.

April 1-2—**Joint Manipulations in Perspective.** UCSF. Friday-Saturday.

April 4-8—**Mental Retardation Institute.** USC. Monday-Friday.

April 5-8—**American Association of Anatomists.** San Francisco Hilton, San Francisco. Tuesday-Friday. Contact: Russell T. Woodburne, executive secretary, The University of Michigan East Medical Bldg., Ann Arbor, Michigan 48104.

April 6-27—**Advanced Funduscopy.** USC. Wednesdays.

April 6-May 11—**Psychiatry in General Practice.** UCSF at Stockton State Hospital, Stockton. Wednesdays.

April 7-June 9—**Ward Walks in Rare Diseases.** USC. Thursdays.

April 12-June 14—**Bedside Cardiology.** USC at St. Vincent's Hospital. Tuesdays.

April 13-16—**American Orthopsychiatric Association.** San Francisco Hilton, San Francisco. Wednesday-Saturday. Contact: Marion F. Langer, Ph.D., executive secretary, 1790 Broadway, New York 10019.

April 14-16—**Retinal Detachment Conference.** Lions Eye Bank. Thursday-Saturday. 8 hours. $100. Contact: Eva del Oro, secretary, Lions Eye Bank, 2018 Webster Street, San Francisco.

April 16—**Sports Injuries.** UCLA. Saturday.

April 16-17—**The Uncertain Quest: The Teen-Ager's World.** UCSF. Saturday-Sunday.

April 21-23—**Endocrinology and Metabolism.** UCSF. Thursday-Saturday.

April 23-24—**Neuropsychiatry for the Non-Psychiatric Physician in General Practice.** UCSF at Sutter Memorial Hospital, Sacramento. Saturday-Sunday.

April 25-27—**Annual Meeting of the Council on Medical Television.** UCSF. Monday-Wednesday. Contact: Irving Merrill, M.D., director, Office of Television Research, UCSF.

April 28-29—**General Surgery.** UCSF. Thursday-Friday.

April 28-29—**Symposium on Hypertension.** USC. Thursday-Friday.

April 29-May 1—**REDWOOD REGIONAL CONFERENCE presented by California Medical Association in cooperation with USC.** Konocti Harbor Inn, Clear Lake. Friday-Sunday. "Cardiovascular Disease, Endocrinology, Office Techniques in Patient Interviews." Chairman: Lucius L. Button, M.D., 1102 Montgomery Drive, Santa Rosa.

MAY

May 1-5—**American Society for Microbiology.** Biltmore-Statler Hilton Hotel, Los Angeles. Sunday-Thursday. Contact: R. W. Sarber, executive secretary, 115 Huron View Blvd., Ann Arbor, Michigan.

May 5-7—**Ear, Nose, Throat.** UCSF. Thursday-Saturday.

May 5-26—**Neuropsychiatric Management in Daily Practice.** UCSF at Modesto State Hospital, Modesto. Thursdays.

May 6-7—**Obesity.** UCSF. Friday-Saturday.

May 7—**Ventura County General Hospital Annual Staff Seminar.** Ventura County General Hospital. Saturday. 6 hours. No fee. Contact: G. K. Ridge, M.D., V.C.G.H., 3291 Loma Vista Road, Ventura.

May 7-8—**Dynamic Measurements with Radioisotope Techniques for Evaluating Organ Function and Circulation.** UCLA. Saturday-Sunday.

May 12-15—**Hawaii Medical Association Annual Meeting.** Arthritis and Psychiatry. Princess Kailuani Hotel, Honolulu. Thursday-Sunday. 15 hours. $35. Contact: Miss Lee McCaslin, executive secretary, 510 S. Beretania, Honolulu, Hawaii 96813.

May 13—**The Modern Cardiovascular Practitioner.** UCSF at Redwood Empire Heart Association, Santa Rosa. Friday.

May 13-14—**Convulsive Disorders.** UCSF. Friday-Saturday.

May 13-14—SAN JOAQUIN VALLEY COUNTIES—**Regional Postgraduate Institute presented by California Medical Association in cooperation with UCLA.** Ahwahnee Hotel, Yosemite. Friday-Saturday. Chairman: Dale Kirkegaard, M.D., 2432 Calaveras Street, Fresno.

May 14—**Humboldt-Del Norte Medical Society Annual Medical Symposium:** "Frontiers in Medicine." Eureka Inn, Eureka. Saturday. 4 hours. Contact: Stanwood S. Schmidt, M.D., president, 707 K St., Eureka.

May 21—**"Clinic Day"—Diseases of Medical Progress.** Channing House Auditorium, Palo Alto. Saturday. 9:00 a.m. to 3:30 p.m. Contact: R. Hewlett Lee, M.D., Palo Alto Medical Clinic, 300 Homer, Palo Alto.

May 21-22—**Health of the School Child.** UCSF. Saturday-Sunday.

May 23-25—**American Thoracic Society Annual Meeting.** Hilton Hotel, San Francisco. Monday-Wednesday. Contact: James Kieran, M.D., chairman, Medical Sessions Committee, American Thoracic Society, 1790 Broadway, New York, N.Y. 10019.

JUNE

June 22-24—**Highlights of Modern Ophthalmology.** Lions Eye Bank. Wednesday-Friday. 8 hours daily. $75. Contact: Eva del Oro, secretary, Lions Eye Bank, 2018 Webster Street, San Francisco.

June 22-24—**Treatment of Fractures.** USC. Wednesday-Friday.

Courses Offered Continuously or by Arrangement

USC:

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Fifty-two issues $100. Physicians may register at any time.

Advanced Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Fifty-two issues $85. Physicians may register at any time.

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TO HAVE YOUR MEETING OR PROGRAM LISTED IN CALIFORNIA MEDICINE

FILL OUT AND MAIL THIS BLANK TO THE ADDRESS GIVEN

(COPY MUST BE **RECEIVED** NOT LATER THAN THE **FIFTH OF THE MONTH PRECEDING** ISSUE)

Continuing Medical Education, California Medical Association
693 Sutter Street, San Francisco, California 94102

NAME OF ORGANIZATION________________

MEETING OR PROGRAM________________

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DATE________________TIME________________

PLACE________________FEE, IF ANY________________

CONTACT FOR INFORMATION:________________
(give name, title, address)

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The Physician's BOOKSHELF

MANAGEMENT OF FRACTURES AND SOFT TISSUE INJURIES — Second Edition — By the Committee on Trauma, American College of Surgeons. Based on An Outline of the Treatment of Fractures, Eighth Edition, 197 pages, published 1965, $3.25; and Early Care of Acute Soft Tissue Injuries, Third Edition, 232 pages, published 1965, $3.50. W. B. Saunders Company, Philadelphia, 1965. 365 pages, $7.50.

This small book is presented as a summary of fundamentals in the management of the injured patient. Its format is that of a well organized outline with a maximum of pertinent rules and facts, and a minimum of discussion or theory. With a scope as ambitious as the title would presume, it must of necessity very briefly allude to much which could be considered applicable to the topic. This is pointed out appropriately by the authors who intend the work as a quick, easily accessible reference source or guide in initial care only. It is divided equally between the treatment of fractures, and the management of soft tissue injuries.

Part I is an outline of the treatment of fractures. The short chapters develop a logical sequence of patient care starting with the initial exam, and carrying through to a very brief note on rehabilitation. This outline is thorough, covering the essentials of patient evaluation and treatment, both emergency and definitive. Specific reference is made to the common fractures of the adult and child, prophylazis against tetanus, evaluation and treatment of shock and infections. A brief remark about the hyperbaric oxygen chamber would have been in order here for completeness. There are, curiously, two separated chapters devoted to anesthesia, the second of which offers very little additional information. Similarly, the short discussion of operative treatment is of necessity so superficial as to be probably unnecessary as a separate chapter.

Part II considers acute soft tissue injuries. Where possible, these are dealt with regionally or systemically so that a maximum of material is covered. In spite of the wide expanse of subject material, the presentation of general principles and fundamentals is balanced well with an adequate complement of detailed information. Thus, one could very capably plan the care of a severely burned patient relying primarily on the information available here.

Chapters on head, neck, spinal cord and facial trauma, vascular injuries, chest and abdominal wounds are also very thorough, and equally effective. The material on hand injuries and amputations is excellent, stressing the fundamentals and avoiding the unnecessary details of operative repair.

Although it is no longer small enough to "fit in the pocket of a residents white coat" as originally intended, the book remains extremely handy and a valuable reference particularly for the emergency room physician, or house officer dealing with trauma. A familiarity with its material would be especially reassuring to the intern or medical student approaching his emergency experience for the first time. A manual such as this is not a substitute for training and preparation, but when fact are figures are clouded by the hour of the evening or the volume of the work, it is comforting to have a familiar source of information readily available. This book could certainly be included in such a source.

Two minor corrections are noted:

1. Page 47, paragraph 3. Induction by inhalation . . . Vs. Induction after inhalation.
2. Page 111, last paragraph . . . a dislocation associated with fracture rarely recurs . . . Vs. . . . rarely occurs.

ROBERT I. BRANICK, M.D.

* * *

MEDICAL MICROBIOLOGY—A Guide to the Laboratory Diagnosis and Control of Infection—Eleventh Edition—Edited by Robert Cruickshank, M.D., F.R.C.P., F.R.C.P.E., D.P.H., F.R.S.E., Professor of Bacteriology, University of Edinburgh; Adviser in Bacteriology, Scottish Home and Health Department, and S.E. Regional Hospital Board (Scotland); Senior Consultant in Bacteriology, Royal Infirmary, Edinburgh. Assistant Editors: J. P. Duguid, M.D., B.Sc., Professor of Bacteriology, Queen's College, Dundee, and R. H. A. Swain, M.A., M.D., M.R.C.P.E., F.C.Path., F.R.S.E., Reader in Virology, University of Edinburgh. The Williams & Wilkins Company, Baltimore, Md., 1965. 1067 pages, $11.00.

This is a textbook by a group of British authors, with Professor Robert Cruickshank as editor. The objective is described as "a comprehensive textbook to cater for the need of all those concerned with the laboratory diagnosis and control of infection in man. We were particularly conscious of the usefulness for countries where communicable disease is still the major contributor to sickness and death, of an all-purpose textbook on medical microbiology which could be a vade-mecum for teachers and students alike. . . ." Of more than 1,000 pages, about 600 are devoted to descriptive bacteriology, virology, mycology and parasitology. The descriptions are fairly conventional, reasonably concise and up-to-date. Major emphasis is placed on laboratory identifications of microorganisms and public health aspects of the subject.

About 400 pages are devoted to detailed outlines of laboratory procedures. In fact, while not describing specific experiments, part of the book can serve as a laboratory manual. Thus 25 pages are devoted to descriptions of the common microscope, 8 pages to "measurement of pH," and 50 pages to the preparation of bacteriological culture media. Streaking of bacteriological plates, incubation and other routine procedures are described in greatest detail.

This book appears to be well suited to teaching and training in countries with relatively low standards of sanitation, public health, laboratory medicine. For many developing countries this book might be an excellent text. It appears less well suited for medical schools in highly organized countries (such as Great Britain or the U.S.) with competent public health, laboratory and hospital services, precisely because it is so largely devoted to the practical and routine aspects of medical microbiology. References are provided at the end of each chapter and there is a comprehensive index.

ERNEST JAWETZ, M.D., Ph.D.

California
Medicine

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KEY TO ABBREVIATIONS USED

(BRP)—Bureau of Research and Planning; (CMA)—California Medical Association; (CR)—Case Report; (CS)—Cancer Studies; (Ed.)—Editorial; (I)—Information; (LE)—Letter to Editor; (Misc.)—Miscellaneous; (Or.)—Original Article; (PE)—Page End; (RSB)—Report of Scientific Board.

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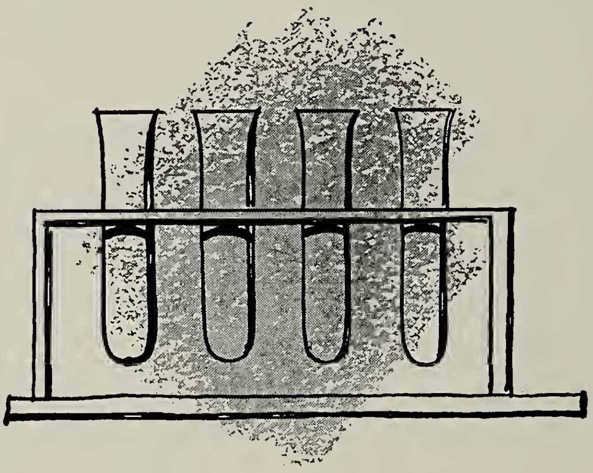

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Before prescribing, consult package circular.

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New Test for Mononucleosis

A faster, more accurate test has been developed for infectious mononucleosis, reports the October 25 *Journal of the American Medical Association.*

The new test can be done in less than two minutes in a physician's office, compared to the 1½ to 5 hours required by the earlier method (which could only be done in a hospital where equipment was available).

The new test further reduces the possibility of misdiagnosis of what some college students jokingly refer to as "the kissing disease." Infectious mononucleosis, whose cause is unknown, seems to be transmitted by close personal contact. It is usually a mild disease characterized by fever, sore throat, and lymph node enlargement.

The importance of correct diagnosis, however, is no joke. Mononucleosis symptoms resemble those of other, more serious diseases, such as acute leukemia, hepatitis, and forms of meningitis and encephalitis. Meningitis, for instance, requires prompt and specific treatment different from that used against mononucleosis; the wrong diagnosis could have serious consequences.

Up to now, the best and most widely used test for mononucleosis has been the Paul-Bunnell test, which is based upon the fact that the blood serum of a person infected with mononucleosis will react with an antigen in the red blood cells of sheep. The serum makes these cells agglutinate, or clump together. Thus, if a person's serum clumps sheep red cells, the diagnosis is infectious mono.

The Paul-Bunnell test, however, is complicated, takes time to perform, sometimes must be followed by another test. Finally, there are an estimated 10 to 15 per cent false positive reactions (indicating a person has mononucleosis when he doesn't) and a smaller percentage of false negative reactions.

The authors of the *Journal* article began looking for a more specific test. Miss Gail Hoff, a doctoral candidate in zoology at Rutgers University and a technician at the Princeton Laboratories in New Jersey, and Stanley Bauer, M.D., of the Princeton, N.J., Hospital, tested several types of animal cells.

Blood cells from horses were found to be the most satisfactory, and the authors developed chemical means of stabilizing them so that they can be furnished in a kit instead of drawn fresh. The Paul-Bunnell test requires fresh sheep cells.

Using the new test in 426 cases suspected of infectious mononucleosis, the correct diagnosis was reached in 98.5 per cent, a far higher percentage than would be likely with the earlier method. In 250 cases, there were false negative reactions in only 0.4 per cent, compared with 9 per cent reported in studies of the older test.

Three advantages of the new test, the authors said, are its low incidence of false reactions, a highly specific reaction to the infectious mononucleosis antibody, and great ease of performance.

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Persantin, brand of dipyridamole, is available as tablets of 25 mg. Two tablets (50 mg.) 3 times daily, at least 1 hour before meals, is the recommended dosage. Clinical response may not be evident before several weeks of continuous therapy.
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No specific contraindications are known. Since large doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension as, for example, in acute myocardial infarction when the blood pressure may be labile. Headache, dizziness, nausea, flushing, weakness or syncope, and mild gastrointestinal distress have been reported.

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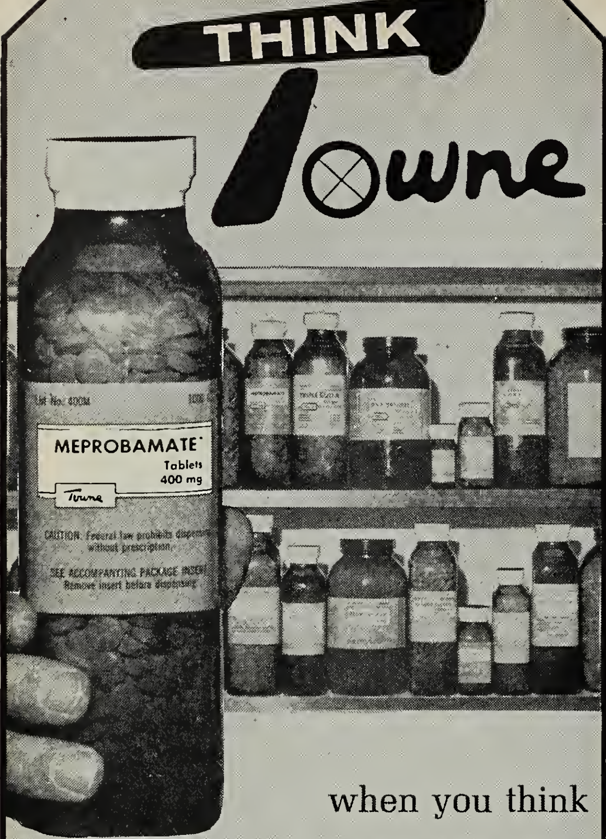

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M.D. Recruitment Successful For Project Viet-Nam

The program director of Project Viet-Nam has reported after a recent tour of South Viet-Nam that the Project's bi-monthly quota of volunteer physicians may soon be "increased significantly."

Dr. Edwin W. Brown Jr., associate medical director of Project HOPE and program director of Project Viet-Nam, said volunteer physicians in South Viet-Nam "are doing an outstanding job and have expressed enthusiasm for assignments."

According to Dr. Brown, some of the Project's 18 doctors now in the Southeast Asian country have said they plan to extend their tours of duty beyond the minimum period of 60 days.

"Because of the success of the program thus far," Dr. Brown reported, "both Vietnamese and American officials have requested that the quota of volunteer physicians be increased as rapidly as adequate facilities can be provided for them."

To meet the increasing demand, Dr. William B. Walsh, president of Project HOPE and The People-to-People Health Foundation, Inc., which administers Project Viet-Nam, said that the number of volunteers per two-month period probably will be boosted to 30 from the present quota of 20.

Dr. Walsh pointed out that more than 100 physicians have applied for service under Project Viet-Nam and another 500 have inquired about the new project.

Project Viet-Nam, created last July at the urging of President Johnson, is financed by the Agency for International Development and aided in recruitment by the American Medical Association.

Under the program, doctors volunteer for a minimum of two months' service without pay, to administer to the medical needs of Vietnamese civilians injured in the war or suffering from the many natural ailments prevalent in that country. The greatest need is for orthopedic surgeons, general practitioners and specialists in internal medicine, Dr. Brown said.

Dr. Brown returned earlier this month from his first tour of Project Viet-Nam activities, which are in operation at Saigon, Da Nang, Bien Hoa, Can Tho, Rach Gia, My Tho, Nha Trang, Qui Nhon, Quang Tri, Bach Lieu, Quang Ngai and Phu Vinh.

In his report, Dr. Brown said that "volunteer physicians are working in a variety of situations in the civilian hospitals, but in each instance the doctor is assigned to work with one or more American doctors or other free world physicians working in Viet-Nam on a long-term basis."

Continuity, according to Dr. Brown, is maintained by integrating the volunteers into the long-term medical teams.

The program director said that doctors interested in serving the Project may submit queries or applications to Project Viet-Nam headquarters at 2233 Wisconsin Ave., N.W., Washington, D.C.

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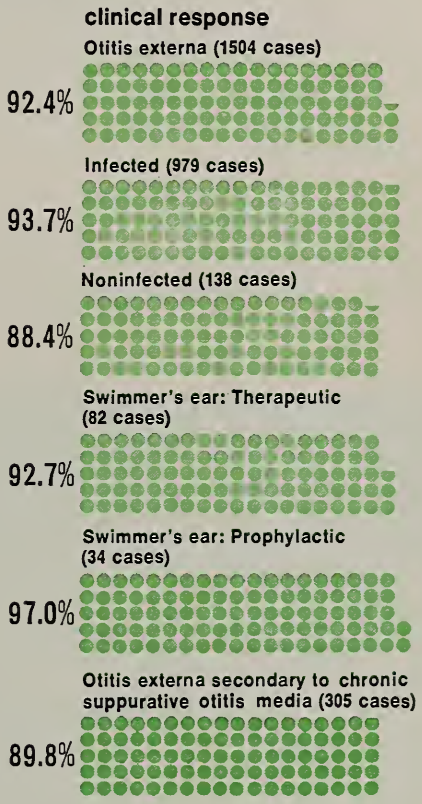
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Within Five Years 14 New Medical Schools

(Continued from Page 32)

when its first class nears the end of the sophomore year.

Rutgers expects to admit a small class in September 1966. Arizona, Brown, Hawaii, Hershey, Michigan State, and South Texas are planning to begin in 1967. All of the 14 schools should be in operation by 1969 or 1970.

Postgraduate Medical Education Expanding

Most physicians continue to study medicine long after entering practice—and the number of postgraduate medical courses available to them has increased nearly 50 per cent in the past five years.

This year, 1,641 courses are being offered in 40 states and the District of Columbia, reports the November 15 *Journal of the American Medical Association.* The issue contains the 65th annual report on medical education by the AMA's Council on Education.

The number of physicians registered in these courses may be over 150,000.

Attending courses, however, is only one of the ways a doctor continues his education, the *Journal* points out. Most physicians rank their continued reading of medical literature as one of their most important sources of new knowledge.

They also continue their education through professional contacts with other physicians, and through hospital staff meetings and national, state and local medical society meetings.

Formal postgraduate courses, however, are becoming increasingly important. Medical schools continue to be the major sponsors, but courses also are offered or co-sponsored by medical societies, voluntary health agencies, hospitals, and governmental health agencies.

The most popular subject when doctors return to class? Psychiatry, by a wide margin. Courses in general medicine come next. Special subject areas such as pathology, surgery, ophthalmology, obstetrics-gynecology, and cardiovascular disease also are popular.

Figures are not now available on the total number of physicians attending continuing education courses. Partial figures indicate that there has been a marked increase since last year.

During the 1964-65 academic year, there were 88,845 registrations at courses sponsored by medical schools. Medical schools sponsor about half the courses. If attendance at other courses was similar, the total registration last year must have exceeded 150,000, the *Journal* said.

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*The references to food groups and to specific amounts of food in this advertisement are those recommended by the Food and Nutrition Board of the National Research Council. Reference material and patient aids concerning proper food selection will be sent to you upon request. Write The Dairy Council of California, Box 2066 C, Sacramento.

Computer Becomes A Blood Banker

For several months, a computer has been keeping the records of a large blood bank in Oakland, California—and it's doing a good job, reports the November 8 *Journal of the American Medical Association.*

The system was worked out by the Blood Bank of the Alameda-Contra Costa Medical Association and Lockheed Missiles and Space Company.

So far, the computer has been able to reduce the bank's inventory of blood 15 to 20 per cent while continuing to serve 28 hospitals with a total of 4,600 beds.

Outdated blood, a costly loss in any blood bank, has been cut from more than 13 per cent of inventory to less than 6 per cent.

As another sign of tightening inventory control, the average age of transfused blood has been reduced from 10.7 to 9.5 days since February 1965.

The system works this way:

Each of 28 hospitals in a two-county area phones its daily blood consumption total to the blood bank, where the information is punch-coded onto paper tape, and transmitted to the Lockheed computer center 50 miles away.

Back from the computer comes a summary of each hospital's report. The computer not only keeps a running total on the blood inventory, but also warns when blood stocks are aging. Losses are cut by transferring this blood to hospitals where it can be used immediately.

Once a week, the computer lists each hospital's average usage by blood type. These reports help reduce inventories to a minimum.

A monthly summary outlines the source and use of every pint of blood. Still another report keeps an eye on human error as data are fed to the computer.

It requires 30 people to handle the 34,000 pints of blood dispersed each year by the blood bank. None of these have been replaced by the computer, the report said, but they have been relieved of the tedium of routine record-keeping.

The computer system is costly, but its efficiencies should repay these costs if widely applied to blood banking, the *Journal* report said. The system's design appears to be applicable to all blood banks, regardless of size or location.

Authors of the *Journal* report are David Singman, M.D., Calisto A. Catassi, C.P.A., and Charles R. Smiley, of the Blood Bank; Willard H. Wattenburg, Ph.D., of the Department of Electrical Engineering, University of California, Berkeley, and Eric L. Peterson, M.B.A., Lockheed Missiles and Space Company, Sunnyvale, Calif. (Mr. Smiley is now with Hyland Laboratories, Los Angeles.)

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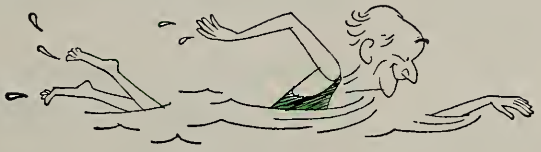

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References: 1. Dufficy, R. G., Jr.: J. Am. Geriatrics Soc. 5:936 (Nov.) 1957. 2. Ende, M.: Southwestern Med. *38*:625 (Oct.) 1957.

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REFERENCES AND REVIEWS

EVALUATION OF A PATIENT ISOLATOR SYSTEM—S. Shadomy (Walter Reed Army Medical Center, Washington, D.C.), M. K. Ginsberg and E. Zeiger. Arch. Environ. Health, 11:652 (Nov.) 1965.

Levels of surface and airborne microbial contamination within a unitized patient isolator were monitored during 12 days of occupancy. In spite of the continued recovery of microorganisms from many of the examined surfaces and fomites as well as from air samples taken within the isolator, no isolations were made for pathogenic species introduced from the hospital environment. The majority of the bacteria recovered within the isolator were equated with organisms of patient origin. The principle source of contamination of surfaces and fomites was found to be fecal in origin. It is concluded from these studies that the isolator was capable of sustaining a patient for prolonged periods with absence of contact with the microbial components of the surrounding hospital environment and to prevent contagion.

* * *

NEW DIRECTIONS IN MENTAL HEALTH PLANNING—L. J. Duhl (NIMH, Bethesda, Md.). Arch. Gen. Psychiat., 13:403 (Nov.) 1965.

In the field of mental health, the community approach toward more effective services has been taken. The planning of comprehensive mental health services, based on the models of disease and growth, must be an interrelated process at federal, state, and local levels. It must cut across old political jurisdictions, agencies, disciplines, and departments, giving priority to services in the urban complex. The new era is one of community organization. It involves the horizontal reorganization of existing community institutions, the emergence of sophisticated counselor familiar with all the community resources, and the participation of citizens in the community programs.

* * *

ACCURACY OF ELECTROCARDIOGRAPHIC MEASUREMENTS BY COMPUTER—R. J. Dobrow et al. (George Washington University School of Medicine, Washington, D.C.). Amer. J. Med. Electronics, 4:121-126 (July-Sept.) 1965.

To assess the accuracy of computer measurement of ECGs, a sample of 200 ECG leads processed by computer was compared with a "standard" established by physician measurement of these leads. Computed measurements were highly accurate. Reproducibility of computer results was evaluated by comparing 10 individual computer runs on a single patient's ECG and by comparing duplicate computations on 20 individual tracings. The very narrow range of results and small standard deviations found, attest to the system's precision. These results provide a basis for confidence in computer identification and measurement of ECG waves.

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